



This work is protected by copyright and other intellectual property rights and duplication or sale of all or part is not permitted, except that material may be duplicated by you for research, private study, criticism/review or educational purposes. Electronic or print copies are for your own personal, non-commercial use and shall not be passed to any other individual. No quotation may be published without proper acknowledgement. For any other use, or to quote extensively from the work, permission must be obtained from the copyright holder/s.

HIV positive refugees/asylum seekers and clinical trials: some ethical issues

Linda McDonald

Doctorate in Medical Ethics

March 2014

Keele University

Abstract

The aim of this thesis was to identify some of the ethical issues of HIV positive asylum seekers and refugees participating in clinical trials in Britain. While all individuals are to some degree vulnerable in clinical trials, I have shown in this thesis that this group is particularly vulnerable in a number of areas. Many will not have English as a first language and while they may be able to understand everyday language, the participant information sheet (PIS) may be difficult to comprehend both in terms of language and content. Cultural aspects may also influence the individuals' participation in a clinical trial. Many will have come from a hierarchical culture where it would be unthinkable to refuse to participate if requested to do so by someone of a higher social status, such as physicians. Individuals may also be reluctant to decline an invitation to participate in a clinical trial if asked to do so by their own clinician, if they are reliant on him/her to provide letters of support for the immigration authorities.

While the clinical trials regulations suggests ways in which the vulnerable can be given additional protection in the research setting, HIV positive asylum seekers and refugees are not always considered by researchers to be vulnerable. As such, the additional protection afforded is denied to them. In this thesis I have suggested a number of measures which will afford additional protection to HIV positive asylum seekers and refugees who participate in clinical trials.

Index

Chapter 1	Introduction	P 4
Chapter 2	Background of HIV and current access to treatment and care for asylum seekers and refugees	P 7
Chapter 3	Clinical trials	P 25
Chapter 4	Value of Asylum Seekers and Refugees as research participants	P 55
Chapter 5	Harms and benefits of participation	P 64
Chapter 6	Consent- provision of information	P 96
Chapter 7	Consent- vulnerability and voluntariness	P 139
Chapter 8	Conclusion	P 176
References		P 185

Chapter 1

Introduction

Before the era of antiretroviral therapy the prognosis for individuals infected with HIV was poor, with many dying within ten years of being infected. Cooper (2008) reports that since the advent of highly active antiretroviral therapy (HAART) individuals who commence on treatment can now expect to live into their sixties. For those who start treatment with a high CD4 count, this increases to seventy years of age. HIV treatment and care is free in the UK under the NHS. However, not all those who are HIV positive are eligible.

In the UK, the Health Protection Agency (2010) reported that out of the 6630 newly diagnosed individuals, 2430 acquired their infection abroad. While many of these individuals will be eligible for NHS treatment and care, a small proportion will not. Following The Court of Appeal Judgement in 'R (YA) -v- Secretary Of State for Health (2009)', it has been increasingly difficult for failed asylum seekers or refugees to continue to access NHS treatment and care. The African HIV Research forum (2010) reported that a small but increasing number of HIV positive individuals had been accessing pharmaceutical industry sponsored clinical trials. Some of these individual were asylum seekers or refugees who had failed their appeal to remain in the UK, and were reported to be entering clinical trials in order to have continued access to treatment and care. The Refugee Council (2006) also reported that some individuals who were in the process of applying for asylum had enrolled in clinical trials. These

individual were under the misapprehension that the immigration authority and health authority automatically shared information, and entering a clinical trial would support their asylum appeal. Anecdotal evidence from HIV clinicians also supports these findings. However, there is little if no documented evidence of the numbers of individuals involved.

While participating in clinical trials may be one means of continuing access to HIV treatment and care for asylum seekers and refugees, there are some ethical issues to be considered. The first two chapters of this thesis will provide the reader with some background information about HIV and clinical trials. This will include HIV transmission, prognosis and treatment and current provision of NHS care for asylum seekers and refugees. Following this, I will go on to discuss the attributes HIV positive asylum seekers and refugees possess which make them invaluable as research participants. I will then discuss the potential harms and benefits of participating in clinical trials, including the role of ethics committees in limiting harm to participants. I will go on to discuss the issue of consent, including provision of information and voluntariness. In the concluding chapter, I will offer some recommendations which will go some way to ensuring that HIV positive asylum seekers and refugees are not disadvantaged by participation in clinical trials.

HIV positive asylum seekers and refugees who have access to NHS treatment and care face different issues from those who do not. While I will address any differences between the two groups in the thesis, the reader should bear in mind that a proportion

of those who currently have access to treatment will become ineligible should they lose their appeal to remain in the UK.

Little has been written on the participation of asylum seekers and refugees in clinical trials in the UK. There may be a number of reasons for this. It is difficult to estimate numbers involved; HIV positive refugees and asylum seekers may not disclose their immigration status to researchers, for fear of being denied access to the trial. Thus researchers themselves may be unaware of the immigration status of the potential participant. Those researchers who are aware that the prospective participant is an asylum seeker may not appreciate that this has any bearing on their participation in the trial. While this thesis focuses on the problems faced by HIV positive asylum seekers and refugees who participate in clinical trials, it is likely that asylum seekers and refugees with other chronic medical conditions will face similar issues accessing on-going medical care.

My interest in writing on this topic stems from twenty-five years of working with people living with HIV both in Africa and the UK. While I have seen great improvements in HIV treatment over the years, accessing treatment remains as much a problem for the vast majority in need as it always has. Having worked both as a researcher in HIV clinical trials, and having sat on a research ethics committee for ten years, I have been increasingly aware of the issues of asylum seekers and refugees accessing clinical trials. I hope that this thesis will highlight some of these concerns and that any recommendations made may seek to address the problem.

Chapter 2

Background of HIV and current access to treatment and care for asylum seekers and refugees

In this chapter I will 'set the scene' for the thesis by providing an overview of HIV including the global and UK statistics. I will go on to outline some of the problems asylum seekers and refugees have accessing NHS treatment and care, and look at how these issues can impact on the health and well-being of the individual.

HIV

In order to understand why having access to treatment is so important to those living with the Human Immunodeficiency Virus (HIV), it is necessary to have a basic understanding of how HIV affects the individual. The discovery of HIV as the cause of Acquired Immune Deficiency Syndrome (AIDS) occurred in 1985. Scientists Luc Montagnier and Robert Gallo were credited as having identified the virus. The identification of the virus followed investigations into a number of unexplained illnesses and deaths affecting gay men in both the United States and Europe. Scientists thought at that time that the virus was sexually transmitted through unprotected anal intercourse. It would be some years before other modes of transmission were identified. As such early publicity campaigns to reduce the spread of the virus were aimed predominately at the gay community. This led to the fallacy - still held by some today - that HIV only affects homosexuals.

Transmission

It is now known that HIV is transmitted in blood, semen, vaginal secretions and breast milk. As such, it can be acquired through unprotected sexual intercourse with a positive individual, passed from an HIV positive mother to her baby through breast milk or during vaginal delivery, contracted through infected blood and blood products or by contaminated injecting equipment. The immune system is responsible for fighting infection. HIV slowly destroys the cells of the immune system, including the CD4 or T. cells. Once the number of cells has been depleted, the individual is no longer capable of fighting infections. Some infections only occur when the immune system is not functioning properly; these are called opportunistic infections, as they take advantage of a weakened immune system. Contracting any one of these infections gives the individual a diagnosis of Acquired Immune Deficiency Syndrome (AIDS). Without effective treatment, people with AIDS will rapidly progress to death. Prior to effective treatment, a person diagnosed with HIV could be expected to develop AIDS within five years. The first antiretroviral medication, Zidovudine (AZT), was licensed in 1990. While this was effective to some extent it was only in 1997, when Highly Active Antiretroviral Therapy (HAART) became available, that physicians were able to significantly extend the life of a person with HIV by delaying the progression towards AIDS. The Lancet (2008) reported on the findings of fourteen cohort studies investigating the long term prognosis of individuals receiving antiretroviral therapy in the West. The report concluded that most individuals taking treatment were expected to live into their sixth decade. The medication cannot, at the present time, eradicate the virus. Once a person has commenced on treatment they

will need to continue to take it for the rest of their lives. While treatment is effective, it can have side effects such as an increase in lipids and blood sugar. There is also a risk of developing drug resistant viruses if the antiretrovirals are not taken correctly or stopped abruptly.

Prevalence of HIV

The UNAIDS (2010) estimate that thirty-three million individuals world-wide are HIV positive, the majority of whom live in sub-Saharan Africa. However, only fifty percent of adults and thirty percent of children who are need in need of antiretroviral medication are receiving it. The Health Protection Agency (HPA) report for 2010 estimated that 86,500 individuals are living with HIV in the United Kingdom. Heterosexuals account for fifty-four percent of new diagnosis in the UK. Of these, sixty-three percent were black Africans, sixty-eight percent of whom had acquired their infection abroad, mainly in sub-Saharan Africa.

There has also been a change in migration over the years to the United Kingdom. Civil wars and resulting poverty have resulted in many individuals leaving their home countries to seek refuge and a better life in the West. Some individuals from former British Colonies came to join family and friends who were already established in the United Kingdom. Others came to pursue a course of study, whilst some sought asylum from oppressive regimes. HIV testing is not readily available in all African countries. As such, many of those newly arrived in Britain will not have had the opportunity to test for HIV prior to their arrival. The Sexual Health Strategy for

England and Wales (2001) set targets to increase HIV testing of all sexually active individuals to sixty percent by 2007. In order to meet this target, HIV testing was actively encouraged in many health care settings such as sexual health clinics, GP practices and antenatal clinics. The Strategy stated that normalising the HIV test and incorporating it into a routine health check would increase the uptake of testing. The British HIV Association (BHIVA) (2008) also recommends that GPs should routinely offer the test when registering new patients. Under the National Health Service (charges to overseas visitors) Regulations (2011) the HIV test is free to all people irrespective of their immigration status, but only those who are eligible for NHS services can access treatment and care. This policy may not be communicated to those invited to test, or even be known to health care professionals offering testing. Concerns around access to treatment may act as a barrier to testing; some people may choose not to test if they would be unable to access treatment should they have a positive result.

Asylum seekers/Refugees

The terms 'asylum seekers', 'refugees' and 'migrants' are used interchangeably in the tabloid press.

Article 1a (2) of the United Nations Convention defines a refugee as:

“A person who has a well-founded fear of persecution for reasons of race, religion, nationality, membership of a particular social group or political opinion and who is outside the country of his nationality or former habitual residence

and is unable or, owing to such fear, is unwilling to avail Himself of the protection of that country or to return to it”

Economic migrants are defined as people who leave their country of origin to seek a better standard of living, but do not fulfil the requirements of the UN convention.

Once a refugee has gained admission to the UK, they can claim asylum under the United Nations Convention Relating to the Status of Refugees (1951). At this point they become eligible for NHS treatment and care. Some refugees and asylum seekers who test HIV positive in the UK may decide to apply to remain in the UK if it is unlikely that they would have access to treatment in their country of origin. Applications by HIV positive individuals to remain in the UK on compassionate grounds are usually made under Article 3 of the Human Rights Convention. Individuals applying to remain under these terms have to prove that they would suffer torture, inhumane or degrading treatment if they were to return to their country of origin. Solicitors for HIV positive individuals argue that being unable to access antiretroviral medication in their country of origin fulfils these conditions, as the lack of proper medical care constitutes inhumane treatment. Without medication it is unlikely that they will continue to enjoy good health, and so will have a reduced life expectancy. However, changes in government policy has made it increasingly difficult for HIV positive asylum seekers and refugees to be granted leave to remain in the UK on these grounds (English, 2005). The Home Office receives country specific reports on the availability of antiretroviral treatment. Based on these reports, they decide if

there is a need for the individual to remain in the UK to access treatment, or if they could access treatment in their country of origin. Soome (2008) challenged this assertion. She found that Home Office reports on the availability of medication were based on flawed information. In many cases where antiretroviral medication was available, supply was sporadic and only a limited range of drugs were available. It may be very difficult, if not impossible, for an individual to have access to the drugs they were prescribed in the UK. This is of particular concern if the individual has some degree of drug resistance. Second or third line treatment may not be available which means that they will not have access to effective treatment.

Antiretroviral Treatment in developed Countries

HAART has been available in developed countries since 1997. HAART consists of three or more antiretrovirals from different classes given in combination. The aim of this combination is to disrupt the replication of the virus at various points in its life cycle. When the virus replicates, it enters and destroys the CD4 cells which are part of the immune system. A reduction in these cells leads to a weakened immune system which is unable to fight infection. People with a normally functioning immune system have a CD4 count of between 500 to 1500 cells per cubic ml (AIDSmap, 2007). Once this drops to below 300, the individual is at risk of developing an opportunistic infection. In order to prevent these infections, the British HIV Association (BHIVA) guidelines (2008) suggest that the optimum time to commence antiretroviral therapy is when the CD4 count is around 350 cells per cubic ml. The BHIVA guidelines state that when initiating treatment, the clinician should weigh up the

benefits of starting treatment with the potential drug toxicity, difficulties with long term adherence and the potential development of drug-resistant virus. If treatment is commenced when the CD4 count is high it could potentially lead to early resistance to antiretrovirals. However, it is possible to access treatment at this early stage as part of a clinical trial where the individual will be closely monitored.

Antiretroviral treatment in less economically developed countries (LEDCs)

In recent years, antiretroviral medication has become available in some LEDCs. However, the range of available antiretrovirals may be limited by cost. In addition, the availability of drugs can be sporadic and individuals are not guaranteed a regular supply, potentially leading to drug resistance. In the West, it costs approximately £8,000 per annum to supply an individual with medication. Due to the Trade Related aspects of International Property Rights (TRIPS) agreement, the cost of medication in the developing world can be as little as \$300 per annum. While this would appear at first to be welcome news, one should remember that this figure may be greater than the annual salary of those living in developing countries. Coupled with high levels of unemployment and ill health, treatment may still be beyond the means of those who need it. Antiretrovirals are seldom free unless supplied through a clinical trial or through international aid schemes. In some cases medication is free, but individuals are still charged a consultation fee which may be prohibitive. Often - when treatment is available - it is limited to members of the countries' armed forces, members of the ruling parties and those with sufficient funds to pay for medical care (Elbe 2005). While trade agreements have resulted in subsidised treatment, the cost of medication

is beyond the financial means of the majority of individuals. The World Health Organisation (WHO) Three by Five Campaign was designed to provide three million individuals with antiretrovirals by the year 2005, but failed to reach its target. In response to this, the WHO set another target which aimed to provide HIV treatment, prevention and care for eighty percent of those in need by 2010. Again, this target was not met. In 2011 the WHO released its global health strategy for 2011-2015. In order to achieve universal access to HIV treatment, it has concentrated on four key areas; reducing new infections by fifty percent in young people, reducing TB related mortality by fifty percent, eliminating new infections in children and reducing HIV related mortality. Meeting these targets is truly daunting. In many developing countries, the infrastructure is seldom in place to ensure that treatment reaches those in need. Hornbeck (2005) describes how corruption at high levels has seen medications destined for out-lying villages in Africa emerge on the black market in Eastern Europe. De Mendoza (2009) voiced concerns that patients may not have access to supporting blood tests that allow physicians to monitor the efficacy and potentially life threatening side-effects of treatment. However, this has been refuted by Mugenyi (2010) who has shown that supporting blood tests may not always be necessary. The problem of provision of antiretrovirals is compounded by emerging resistance to the virus. In order for treatment to be effective, drug levels in the blood need to be kept within a specific level. This is achieved by taking antiretrovirals at regular intervals throughout the day. The BHIVA guidelines (2008) states that unless ninety-five percent compliance is achieved, the virus will become resistant to antiretroviral medication. Should this occur, the individual will need to change to

another class of antiviral therapy which may not be available in resource limited countries.

Access to NHS services

The rules relating to access of NHS services for asylum seekers and refugees has been changed repeatedly over the last few years, leading to confusion for both patients and clinicians. National Health Service (charges to overseas visitors) regulations (2011) stated that asylum seekers whose application to remain in the UK failed, and all appeals have been exhausted, were only eligible to limited NHS care. This included emergency treatment in accident and emergency services, compulsory psychiatric treatment and treatment of infectious diseases, excluding HIV. HIV is not considered to be an 'infectious disease' in this instance as it cannot be communicated passively from one person to another. For example, pulmonary tuberculosis, which is considered to be an infectious disease, can be contracted from sitting in close proximity with someone with an active infection. This is not true of HIV, which can only be communicated if the individual were to have unprotected sexual intercourse with the person sitting next to him or sharing equipment related to the taking of drugs.

The changes relating to NHS treatment and care followed the court decision of *Shah v Barnet London Borough Council* (1983) 2 AC 309, where an asylum seeker or refused asylum seeker, who had been granted temporary admission pending further action (including removal) on his or her case, could be considered an ordinary resident of the UK. The Secretary of State can make regulations for certain types of

health services to be charged. He can also make regulations for people who are not regarded as having 'ordinary residence' to be charged. Ordinary residency means that an individual must be living in the UK lawfully, voluntarily and as part of the regular order of his or her life. In 2008, Mr A, a failed asylum seeker, was refused access to NHS treatment. Mr A appealed and the case was heard by Mr Justice Mitting. The case, *A v Department of Health and West Middlesex University Hospital NHS Trust* (2008), found that the ruling was wrong in failing to recognise a refused asylum seekers' right to free treatment despite the 1989 Regulations. Asylum seekers who met the ordinary residents test were eligible to receive NHS care.

In response to the findings from the review, the BMA produced guidelines for doctors (The BMA, 2008). These stated:

The Department of Health guidance was judged to be unlawful in not stating that refused asylum seekers can be considered 'ordinary resident' in the UK. The resultant ruling makes it possible for asylum seekers whose application has been unsuccessful to be considered 'ordinarily resident' in the UK and therefore entitled to free NHS hospital treatment.

In effect, failed asylum seekers who were considered 'ordinarily resident' in the UK were now entitled to free NHS hospital treatment. Unfortunately, this ruling did not cover all asylum seekers and refugees, as some were not considered 'ordinarily resident'. This group was still not eligible for free NHS treatment and care. In addition,

the guidance from the Department of Health (2008) on what constituted an 'ordinarily resident' remained unclear, leaving it to the discretion of individual NHS Trusts to decide who could and could not access services. The Department of Health appealed against the ruling. The Court of Appeal (2009 ECWCA CIV 225) rejected the High Court's approach, finding that refused asylum seekers could not be lawfully resident in the UK. However, the Court of Appeal found that the current guidance in relation to the interpretation of 'urgent' and 'immediately necessary' treatment was too restrictive. Patients who could no longer argue that they were lawfully resident in the UK could access treatment by arguing that they need it because it is urgent or immediately necessary and that they were unable to return home at the present. They would still liable to be charged but treatment could not be refused if they could not pay.

The 2009 ruling meant that NHS Trusts could again charge refused asylum seekers for treatment. They had the discretion to initiate treatment prior to payment if the individual could not (as opposed to would not) pay. The Department of Health guidance in relation to when people should receive treatment if they could not pay and could not return home had been deemed unlawful under The Court of Appeal ruling (2009 ECWCA CIV 225). Hospitals could not use the guidance to refuse to treat patients. If they did so they would be acting unlawfully. However, the guidance was interpreted differently by NHS Trusts and there remained inequity of the provision of treatment.

How did this relate to failed asylum seekers who were HIV positive? HIV positive asylum seekers and refugees were unclear if they were eligible for NHS treatment and care at their hospital. Those individuals who commenced treatment prior to having their asylum claim rejected were able to continue treatment until such times as they left the country or the course of treatment concluded. However, they were charged for any new courses of treatment. Unfortunately, changes to antiretroviral medication are quite common due to side effects or the development of drug resistance. THT (2010) reported that some NHS Trusts were interpreting a change of antiretroviral regime as starting a new course of treatment, and charging patients. This interpretation of the guidance caused confusion for both health care staff and patients. The British Medical Association (BMA) (2011) stated that doctors should not be expected to assess the eligibility of their patient to free NHS care. The BMA suggested that this responsibility should be left to administrative staff. In reality, the staff responsible for administering the legislation had no clinical knowledge. While doctors did not want to be involved with assessing eligibility criteria, their input was essential to ensure that administrative staff did not interpret changes of antiretroviral medication as commencing a new course of treatment. The change to the law provided a challenge to advocates from HIV support groups, who had to assess each individual case on its own merits. THT reported that while each case was being assessed, some patients experienced an enforced treatment break, potentially leading to the development of drug resistant HIV.

While the changes to treatment could still be denied under the NHS, clinical trials

continued to be funded by the pharmaceutical industry. As such, individuals who were unable to access or change their medication under the NHS would be able to do so as part of a clinical trial. Information regarding new HIV clinical trials and inclusion criteria were published by HIV organisations such as the National AIDS Trust, and were readily accessible to all patients. The change in eligibility may have contributed to the reported increase of failed asylum seekers seeking to enter HIV clinical trials as a means of continuing to access medication.

Caring for those patients who no longer had access to treatment and care was challenging for medical staff. As discussed earlier, many of the failed asylum seekers and refugees had been diagnosed in a sexual health clinic and would have continued to remain under the care of the HIV team led by the consultant. Like other chronic medical conditions, HIV patients see their doctor on a regular basis. In addition to the clinical care of the patient, doctors are actively involved in both the psychological and social aspects of care. They will have discussed the effects of HIV on patient's relationships. They will have offered support to the patient when they disclosed their HIV status to family members and will have been involved with testing partners and children, in addition to arranging support to the extended family over a period of time. They will have attended multidisciplinary meetings and will be aware of the effects of HIV on the patient's social situation, such as housing and benefits. The doctor may have been one of the first to know that an asylum claim has failed and will have been acutely aware of the clinical implications if their patient is no longer eligible for treatment. Some physicians may have been able to continue to prescribe treatment

due to the inconsistencies in the interpretation of the legal rights of failed refugees and asylum seekers. Others would have been informed by their NHS Trust that as the individual was no longer eligible they could no longer continue to provide treatment and care. While the individual may not have been eligible for treatment and care, there was - and continues to be - a significant delay between the notification of a failed asylum appeal and deportation. Amnesty International (2006) reported that asylum seekers and refugees who had exhausted all their appeals were expected to leave Britain within twenty-one days. However, there were often delays with some individuals remaining in the Britain for as long as ten years. During this time the individual would not be eligible for NHS care and would very likely experience deterioration in their medical condition. While it was difficult for the doctor to continue to prescribe NHS care without falling foul of the authorities, he could suggest that the individual consider enrolling in a clinical trial as a means of continuing treatment. While there was limited evidence to suggest that this was common practice, Hamill (2004) found that some doctors had reported doing so. Continuing to access treatment via a clinical trial may have been one means of accessing treatment but it was not a viable option for all. The patient may not have fulfilled the inclusion criteria of the trial, or they may not have been a suitable clinical trial running in a site within travelling distance. Encouraging patients to access clinical trials as a means to continue treatment did not address the main issue which faced doctors at this time. They were in effect being asked to withdraw medical care to an individual with whom they had an established duty of care. This was not based on the availability of treatment but on a legal principle. The 1951 Geneva Convention relating to the Status

of Refugees requires host countries to provide only basic standards for treatment for refugees. The host countries are free to apply additional domestic law at their own discretion, which the British government had done in this situation. Their argument that they were fulfilling their statutory obligation in regard to treatment and care was met by derision from most clinicians. While I do not intend to discuss the rationale for the government's decision here, many clinicians felt that this was driven more by political pressure to be seen to be 'tough' on refugees than by any financial consideration. No matter what the reason, the effect of the policy would mean the physical and psychological decline in health for a substantial number of individuals. It was gratifying to see the response from clinicians and the voluntary sector to the new law. Many clinicians declared that they would continue to prescribe as before and were prepared to be taken to court over their decision, stating that it would be unlikely that any court would find against a doctor who was caring for his patient. They argued that while they accepted that the NHS had limited funds, to deny lifesaving treatment was in conflict with the principle of non-maleficence. Others argued on more pragmatic grounds. Without access to treatment, HIV positive individuals would soon succumb to opportunistic infections, many of which require admission to an ITU department, which was covered in the change as emergency care. The cost of treating an individual in ITU would be significantly more than providing on going HIV treatment and care. Meanwhile, the HIV voluntary sector lobbied politicians and challenged the media view on the treatment of asylum seekers and refugees. I strongly supported both the actions and the arguments given by the clinicians. However, I could not help but reflect that the government's decision to the withdraw

treatment affected only the most vulnerable in society, namely refugees and asylum seekers who are additionally burdened by having a potentially life threatening medical condition. Any attempts by the government to impose a policy denying lifesaving drugs to the general public would be met with an outcry. While it could be rightly argued that there are restrictions on some drugs under the NHS, patients can access alternative treatments. At present, the only effective treatment for HIV is antiretrovirals.

Refugees and asylum seekers have few political rights, nor are they regarded in a sympathetic light by the media. With the duty to accept refugees into a country comes the duty to treat them humanely. Withdrawing medication which will lead to ill health and eventually death cannot conceivably be regarded as humane treatment. Some might argue that once an asylum seeker or refugee has had their appeal rejected, Britain no longer has any statutory obligation to continue to care for them. While this may be correct under the letter of the law, the fact remains that it may take several months - if not years - before they are eventually deported. These individuals do not have any money and cannot purchase a ticket back to their country of origin; they are prohibited to work, and have no legal means of raising the funds to buy one. As such, I would argue that until the process for deportation has been improved, the government must either continue to care for failed asylum seekers until they are deported, or to relax the employment laws allowing them to work to support themselves. The latter will also enable them to pay National Insurance and contribute towards the cost of treatment. We cannot claim that we are a progressive and tolerant

country if we stand back and let the most vulnerable people die for lack of drugs which are readily available.

Following vociferous campaigning, the NHS (charges to Overseas Visitors) Regulation was amended yet again. From the 1st October 2012 HIV positive asylum seekers and refugees who had had their asylum appeal rejected were now eligible to continue to access HIV treatment and care until they had *been* deported. However, the changes do not include treatment for other health conditions which remain chargeable. While this change was welcome news, THT has shown that a number of HIV positive asylum seekers are still unaware that they can now access treatment and care. More concerning, a number of NHS Trust also seem to have limited understanding of the new changes. A number of HIV positive individuals are still enrolling in clinical trials as a means of continuing treatment. One participant, who has been waiting for a ruling on his asylum appeal for some time, commented 'I have seen so many changed in the law over the last few years. I would rather be sure of getting my medication this way (clinical trial) than be stressed about any more changes.'

Conclusion

This section has briefly outlined the background to the provision of HIV treatment to asylum seekers and refugees in the UK. HIV treatment is complex and constantly changing as our knowledge and understanding of the virus increases. We now have the ability to treat those living with HIV, but as of yet are unable to eradicate the virus.

Also changing is the social context for treatment, and how it affects the lives of those affected by the virus. For those failed asylum seekers and refugees who test HIV positive in the UK, life can be very challenging. Liberty (2008) outlined some of the issues facing these individuals; they are not permitted to work and are unable to buy the nutritious food needed for their continued good health. They may have to rely on friends and charities to provide shelter. For those who are on treatment the decision to remain in the UK is not one they take lightly. While they may remain physically well, they are apart from their family and friends. Those who decide to return home may not be able to access to treatment and will see deterioration in their health. While HIV positive asylum seekers and refugees are now eligible to NHS treatment and care, there remains confusion about eligibility both from patients and those providing care. As such some individuals may choose to continue to access antiretroviral therapy via a clinical trial.

Chapter 3

Clinical trials

In this chapter, I will provide the reader with a basic understanding of clinical trials which will inform the next chapters of this thesis. I will begin by outlining the background to clinical trials legislation and the rationale for conducting trials. I will go on to describe the different types of clinical trials. I will give a brief overview of the process required to gain ethical approval for clinical trials in the UK.

Background to clinical trials

Twyman (2004) provides a brief history of clinical trials. Prior to 1900, there was little legislation to govern clinical trials. Research tended to be conducted by physicians who were also responsible for the general medical care of the patient. It was unusual for the physician to fully inform the individual that the treatment was new, or to seek consent from them prior to commencing research. While patients were aware of this practice, the high regard in which doctors were held resulted in few concerns. Patients were much less likely to question the judgement of their doctor, expecting him to act in their best interest. In 1900, Prussia drew up the first regulations about non-therapeutic research Vollman (1996 p.1445). Under the Berlin Code of Ethics (1900), the Royal Prussian Minister of Religion, Education, and Medical Affairs guaranteed that:

All medical interventions for other than diagnostic, healing, and immunization purposes, regardless of other legal or moral authorization are excluded under all circumstances if,

- i. the human subject is a minor or not competent due to other reasons;
- ii. the human subject has not given his unambiguous consent;

This followed on from concerns that prisoners were being used as research participants without their consent. Weimar Germany followed with guidelines for new therapy and human experimentation in 1931 Rothman (1992, p. 320).

More structured regulations on research followed the Nuremberg war trials in 1947. Katz (1996) reflected on the treatment of individuals who had been imprisoned under the Nazi regime for both criminal and socio-ideological reasons, such as Jews and homosexuals. These individuals had been subjected to the most appalling clinical experimentation. These experiments, conducted by medical practitioners without the consent of the individual, endangered the individual's lives and future well-being. The doctors who had conducted the trials were brought before a military tribunal in the city of Nuremberg. They argued that while the experiments were conducted without consent from the individuals and caused undue harm, they were justified as the information gained would have had long term scientific value. This view was not shared by the tribunal, who found that their research had no scientific merit and was

little more than torture. Those found guilty of involvement were sentenced either to death or were given long term prison sentences. Following the Nuremberg trials in 1946, a code of conduct for researchers involved in clinical trials was drawn up. This was initially called the Nuremberg Code (U.S. Gov Printing Office 1949, p.181) which set out ten principles that physicians were expected to follow when conducting research on humans. The first principle underlined the need to obtain informed consent from the individual prior to his participation in any clinical trial; the individual had the right to discontinue participation in the trial at any time. The code went on to outline the need for the experiment to yield fruitful results. Researchers were expected to conduct trials on animals prior to research in humans. When conducting trials in humans, they were to ensure that participants did not experience unnecessary suffering. They were also expected to ensure that the trial would not result in death or debilitating injury. Research was to be conducted only by scientifically qualified individuals. The researcher also had to ensure that participation in the trial would be terminated at any stage if the individual was at risk of injury, disability or death. The principles of the Nuremberg Code were incorporated in the Declaration of Helsinki, set out by the World Medical Association in 1964 (WMA 1964). The requirement of clinical trials to be reviewed by an independent ethics committee was added to the Declaration of Helsinki in 1975 (WMA 1975, 1.2). The Declaration has been amended over the years to accommodate the increasing changes in medical knowledge, such as the genetics (WMA statement on Genetics and Medicine, 2009). However, the protection of the individual participant remains at its core. In the UK, the Medical Research Council (MRC) issued its first statement on

'Responsibilities in Investigations in Human subjects' in 1963 (MRC 1963). This was intended to provide additional information and support to medical practitioners who were involved in research. The MRC continues to update its recommendations to this day and provides written information on all aspects of clinical trials for investigators.

In response to the Declaration of Helsinki, the Royal College of Physicians (RCP) in the UK produced a report proposing that research ethics committees (RECs) were to be formed. The recommendations were issued in 1967 and distributed to those concerned with research by the Department of Health (Rosenheim 1967, p.429). By 1975, the Department of Health and Social Security had endorsed the RCP proposals on the setting up of ethics committees. This opened the way for hospitals and universities to establish local ethics committees. The purpose of RECs was - and still is - to ensure that the research participant is protected from injury, distress or discomfort. RECs also protect the researcher from litigation by ensuring that any research is conducted with regard to current legislation and will protect the good name of institutions where the research is being conducted, by ensuring that the researchers meet any required standard (RCP, 2007). In 1984, The Royal College of Physicians published its first 'Guidelines on the Practice of Ethics Committees in Medical Research' (RCP 1984), which was helpful to those involved with the setting up of these committees. However, there was no uniformity between different ethics committees. This was rectified in 1991 when the Department of Health produced a document outlining how research ethics committees should be organised (DOH, 1991). Researchers who intended to conduct research at more than one site were

expected to submit identical applications to local research ethics committees at each site. This was very burdensome for the investigator and caused long delays in gaining ethical approval. In order to rectify this problem, Multi-Centre Research Ethics Committees (MRECs) were established in 1997 (DOH 1997). The MRECs were managed by the newly established Central Office of Research Committees (COREC). COREC was subsumed within the National Patient Safety Agency in 2005 and is now known as the National Research Ethics Service (NRES).

Rationale for HIV related trials

World economy

Undoubtedly, HIV is a growing global health concern. It has been estimated that over twenty million people have died due to AIDS-related causes. The UNAIDS (2007) estimates that there are now forty million people living with HIV world-wide. Of those, two million are children. The health impact of HIV can also affect the economic development of countries. The UNAIDS (2007) estimates that ninety percent of HIV positive individuals live in less economically developing countries (LEDCs).

The World Economic Forum conducted a survey amongst company chief executives to establish the level of concern they were experiencing regarding the impact of HIV on their businesses (WEF, 2006). Eleven thousand companies were contacted in one hundred and seven countries. Over half of those contacted responded. Most said that HIV was already having a negative impact on their businesses, and were concerned that this could get worse in the future. They cited several areas of concern. The first

was the effect HIV had on the physical health of the individual employee. Individuals at the highest risk of contracting HIV are those in their peak economic production years. Around half of all HIV positive individuals become infected by age twenty-five and die of an AIDS related illness before they reach their thirty-fifth birthday (WHO, 2006). HIV is a progressive illness characterised by periods of ill health. During this time, the employee will most likely have prolonged periods away from the work place - either for hospital visits or to recover from HIV related infections. This was of particular concern to those companies which employed skilled workers, such as engineers. Companies often support workers to gain additional qualifications. In return, they are expected to use their newly acquired skills for the benefit of the company. If the employee is unable to work through ill health, the company loses both the investment they have made in that individual and any future contribution they would have made. The loss of one employee may not place great burden on the company. However, the rising prevalence of HIV suggests that a high proportion of the workforce will become affected. As it takes time to train a skilled worker, the company may not be able maintain a skilled work force as employees become too ill to work. This will have a detrimental effect on the ability of that company to meet targets and compete in the market place. If this pattern is reflected in other industries, HIV could affect the economic stability of countries in the developing world. The World Economic Forum estimates that by 2015, four million people who could be eligible for work will be unwell due to HIV infection (WEF, 2006). These individuals will be unable to sustain full-time employment. The WEF goes on to project that without access to effective treatment, forty-eight million of the world wide labour force

will be lost to HIV by the year 2010. This projection is increased to seventy-four million by the year 2015. Some may ignore the AIDS epidemic, thinking that it will have no personal impact on them. However, economically developed countries rely on LEDCs to supply them with raw materials and cheap manufactured goods. Hecker (2009) reported on the potential effects of HIV on LEDCs. She stated that it is likely that without affective treatment for HIV, LEDCs will be unable to continue to meet the demand of the West. Farmers will be unable to tend their crops, leading to a reduction in the supply of food stuffs. There will also be a shortage of skilled teachers to educate the next generation who will be needed to replace those already lost to the virus. HIV will also affect public sector workers such as the police, which will have a negative impact on handling crime. Avert (2006) reported that health care workers such as doctors and nurses will also be affected. By 2005, Botswana had lost seventeen percent of its health care workers due to AIDS. UNAIDS (2006) reports that this loss is reflected in other African countries, further reducing the health care provision to an already desperate people. It is likely that without cost-effective treatment, HIV will negatively affect the global economy, impacting society as we know it.

Accessing treatment is not a viable option for the majority of those living with HIV in LEDCs. Only twelve percent of those needing HIV medication in the developing world receive treatment (WHO, 2008). The most compelling reason for the lack of access to treatment is the affected countries inability to pay. When a drug has been developed, the pharmaceutical company can apply for a patent. During the life of the patent no

other company is permitted to produce that drug. The companies are able to set the cost of the drug at a level calculated to recoup the cost of development. In the United States of America a drug patent lasts for twenty years. However, the clock starts when the clinical trial begins, so in effect the patent may be effective only for seven to twelve years. This time frame may differ in other countries. There have been moves by several developing countries to break these patents. This would enable generic HIV treatments to be manufactured at a fraction of the cost, making them more accessible for those who need them. These initiatives have the backing of the former president of the USA, Bill Clinton (Guardian, 2008). The Health Minister for Thailand stated that at present, their Government is only able to provide HIV drugs for a fifth of the population which needs them (Guardian, 2008). However, if they were able to manufacture generic brands, it would be possible to provide treatment for a greater number of the population. This in turn would have a positive impact on the economic development of their country. The World Trade Organisation (1994) issued a directive which enabled governments to issue compulsory drug licenses for non-commercial use in the case of national emergency. The steadily increasing levels of HIV and the negative impact this has on the economic development and health of nations could certainly be deemed a national emergency. Despite this agreement, countries which produce generic HIV medications could face trade sanctions. If the pharmaceutical companies continue to demand intellectual rights and sanctions are placed on countries which develop generic HIV drugs, the impact on the world economy will continue to be devastating. Pharmaceutical companies argue that the cost of developing new medications is so high that they must rely on the income from these

drugs to recoup research and development costs. Loss of this income will affect both the company and those who have invested in it, thus delaying the development of other potentially lifesaving drugs. Pharmaceutical companies are concerned by the increasing trend of developing countries producing generic versions of patented drugs. Brazil is the most recent country to issue a compulsory license to begin to import a generic antiretroviral. The proposed move to import the generic version of Efavirenz, one of Brazil's most widely used HIV drugs, has been condemned by the parent company Merck. Merck issued a statement in which it said that this 'sends a chilling signal' to companies of the risks of developing drugs which are used in the developing world. The statement went on to say that pharmaceutical companies 'cannot sustain a situation in which developed countries alone are expected to bear the cost for essential drugs' (Massarani, 2008). This may deter them from future investment in developing new HIV treatment.

There have also been concerns raised that generic medications are not as effective as those manufactured under patent. There have been reported incidences of viral rebound, and the development of multi-drug resistant strains of the virus developing in those taking generic HIV medications (Avert, 2006). The reason for this may be multi-factorial. It could be, as the HIV organisations claim, that the antiretrovirals do not have the same potency as patented treatment. The World Citizens Advice Bureau (2005) reported that the World Health Organisation had removed some generic brands of HIV medication from its quality assurance list following irregularities in clinical trials, which were designed to show that generic HIV medications are as

effective as patented ARV's. Even if the generic medications were identical to the branded product - both in content, strength, safety and efficacy - the infrastructure designed to ensure that clients are aware of how to correctly take the medication, and how to limit the potential for drug resistance may not be in place in some countries supplying generic medication. No matter what the reason, the need for effective, easily administered, cost effective antiviral medication cannot be denied. Pharmaceutical companies should not be discouraged from investing in new medications. This must be balanced against the urgent need to provide treatment to those who need it. As the effects of HIV continue to affect world economy a global solution is needed. I suggest that new strategies are needed. These could involve financing drug development at a national or global level. The cost for research, development, production and supply of HIV treatments could be shared by countries, thereby reducing the devastating effects of HIV on the world economy. This in turn would enable pharmaceutical companies to continue development without fear of loss of income.

Economic impact on families

While we have seen the effect HIV has on the global economy, some groups bear a disproportionate burden of the disease. Women in particular are greatly affected by HIV WHO, (2009). While the role of women in the family has changed over the years, most societies still expect that women will be responsible for managing the welfare of the family. In LEDCs this role is more exacting than that expected of western women. In addition to normal household chores, women in LEDCs may be expected to tend

the fields and sell any excess crops they grow; this raising money to provide food for the family and educate their children. The women may also have to travel long distances to source fresh water or food. Women not only care for the needs of the nuclear family, but also that of extended family members. If a family member becomes unwell, the burden of caring for them will fall on the woman. The time spent caring for them may impact on her ability to fulfil her other duties, such as looking after crops. The income which she receives from farming will be substantially reduced, leading to lack of food and increased poverty. Any savings she has may be spent on health care, causing additional worry and more financial burden on the family. Should she contract HIV and become unwell, she may find it impossible to continue to care for her family.

Due to gender inequalities, women often have little say in their personal lives. HIV prevention schemes are often aimed at women, giving them information about harm reduction. However, unless their husband is in agreement, it is unlikely that they will be able to insist on the use of condoms to prevent transmission of HIV and sexually transmitted infections. Gender inequalities also make it difficult for them to access HIV treatment. If there are limited funds available to the family, it is likely that these will be used to purchase medication for the male partner before the women or children (Matlin, 2000).

There are many types of clinical trials taking place in HIV. Some researchers are looking into the development of vaccines which may prevent onward transmission of

HIV. Researchers are hoping that a single course of the vaccine may be able to significantly reduce the risk of HIV transmission. If vaccine trials were successful, they would be particularly beneficial to women. Even if women were not in a position to negotiate safer sex with their partners, the vaccine may protect them against the virus. It is likely that if a vaccine were to be developed, a single course to prevent transmission would be much more cost effective than becoming infected and having to take life-long medication. As such, the development of new HIV treatments will benefit both the individual and have a positive impact on developing economies.

Impact on children

HIV has the greatest impact on children. Avert (2007) estimates that more than fifteen million children worldwide have been orphaned due to AIDS. Some of these children will be infected themselves. I want to look first at children infected by HIV. Connor et al (1994) found that the risk of vertical transmission to the child can be reduced to less than one percent in a pregnant woman if she takes antiretroviral therapy in the last trimester of pregnancy. However, in LEDCs the availability of medication is restricted to those who can afford treatment, or those who are fortunate enough to access government programs or as part of an HIV clinical trial. Without antiretroviral medication in pregnancy, twenty-five–forty percent of children born to HIV positive mothers will be positive (AIDS MAP 2007). As such, three-quarters of a million children each year are infected by the virus through maternal transmission (UNAIDS, 2007). Even if the virus has not been transmitted during pregnancy and childbirth, the child may still be at risk of contracting the virus via breast milk. Coovadia et al (2007)

identified specific risks relating to HIV transmission via breast milk. They found that in women who breast feed exclusively for six months, the risk of transmission to the child is around four percent. However, if the baby is mix-fed, it is eleven times more likely to become infected. The study also found that babies who are exclusively breast fed for six months were more likely to survive than those fed formula alone in the first three months. As such, the WHO (2009) is now recommending that HIV positive mothers who are unable to afford formula breast feed exclusively for six months. While this guidance may help to reduce HIV transmission, it may not be readily accepted by mothers. UNICEF (2009) reports that mixed feeding is common in LEDCs, with breast feeds being supplemented with water, tea and porridge within the first few weeks of life. Mothers are often concerned that their breast milk will not provide sufficient nutrients to their babies if they themselves are malnourished. If exclusive breast feeding initiatives are to be successful, women will have to be convinced that their babies will not be harmed.

Should the child become infected, without access to treatment they have a poor prognosis. AIDSmeds (2008) estimates that most infected children will die before their fifth birthday. However, with access to treatment and care, approximately half of all children will live to graduate from high school. With the advances in HIV therapy, the prognosis of children undergoing treatment is looking increasingly bright. Unfortunately, children are less likely to have access to HIV treatment programs than adults. Parents may be too unwell themselves to tend to the medical needs of their children. It may be impossible for sick parents to transport equally sick children to a

hospital some distance away. The parents may be unable to provide the child with enough nourishment to enable them to withstand infections. When the parents can no longer look after their child, it may be placed in the care the extended family. The extended family may be in no better position to offer care than the parents. While they may be able to provide shelter and food, they may not be able to fund treatment.

Even without antenatal treatment, only twenty-five percent of infants born to HIV positive mothers will develop HIV (WHO, 2011). HIV negative children born to HIV positive mothers can also be affected by HIV. Stein (2003) found that young children whose parents were HIV positive had to take on responsibilities beyond their years. This included physical care of parents and other siblings, in addition to providing psychological support. A study conducted by the WHO (2007) found that these children often had to leave school in order to look after their parents. In addition to providing care, they often worked part-time in order to earn money to support the family. The loss of a normal childhood affected the children's psychological development. Having to abandon their education impacted on the child's future ability to find skilled work. The World Education Fund (WEF 2007, p31) found that HIV infection in the family affects literacy rates in poorer countries. Without the ability to read or write, employment prospects are reduced. This in turn perpetuates the cycle of poverty.

Children orphaned by AIDS are at greatest risk from poverty. Traditional African culture expects the extended family to support each other. Orphaned children are

provided with love, food, shelter and education. However, as the number of people infected by HIV rises, it becomes difficult for families to support the increasing number of those in need (Avert, 2011). Some children may be fortunate to have relatives who can support them. For many families the desire to help remains, but they are financially unable to provide care for all in need. Some children may have access to care provided by charities. For the majority however, the future is not so bright. UN AIDS (2007) estimates that only ten percent of AIDS orphans receive public support or services. The children lack basic needs such as shelter, food, and clothing. In order to survive, some turn to a life of crime. Others survive by forming an association with other children in the same situation, scavenging for food and surviving from hand to mouth (Salaam, 2005).

Without cheap, effective treatment HIV will continue to have devastating effect in LEDCs. The number of deaths will continue to rise, as will the number of people who are too ill to work. This will have a knock on effect on the global economy. While the 'holy grail' of HIV research is to develop a cure, it is unlikely that this will happen in the near future. In the meantime, research is essential to advance our knowledge of HIV and develop more cost-effective treatment with a better resistance profile. The more information we can gain about the virus through research, the greater the chance we have of reducing onward transmission. New treatments would not only improve the lives of those living with the virus, but have a positively influence on the global economy.

HIV undermines the global efforts to reduce poverty and promote development. This was summed up succinctly in 2006 by the World Economic Forum:

Affecting predominantly young and middle aged adults who are the mainstay of the economic and principal support of their families- AIDS destroys the fabric of society

Why conduct HIV clinical trials in the UK?

While very few would deny the need for clinical trials to develop effective HIV treatment, some would argue that there is no need to conduct this type of trial in the UK. The number of HIV positive individuals in the UK has steadily risen over the years, but in comparison to the developing world the figures are small in comparison to the developing world. UNAIDS (2008) reported that forty million people world-wide were infected with HIV. Twenty two million of those affected live in sub-Saharan Africa, while only one million live in Europe. These figures illustrate that there are more people living with HIV in Africa, and therefore more potential recruits for clinical trials. As access to antiretroviral therapy is limited, it is likely that potential recruits will have had less exposure to treatment. As discussed earlier, those who are antiretroviral naïve are much better candidates for new HIV clinical trials. As such, HIV positive individuals from sub-Saharan Africa are more likely to possess the biological assets required by researchers than their counterparts in the West who are likely to have had previous exposure to antiretrovirals.

In the UK, it can take up to sixty days from submitting a trial proposal to receiving ethical approval (NRES 2009). This does not include the time taken to prepare the application nor write the patient information sheet. Only once ethical approval has been received, can the company begin to set up the trial and begin recruitment of trial subjects.

In the developing world, the process of gaining ethical approval may be much faster. As such, set up and recruitment can begin earlier. Goggins (2005) reported that the development of a new drug can cost a pharmaceutical company around £550 million. If companies are struggling to recruit the required number of participants, any delay in completing the clinical trial will result in additional costs. Having a greater pool of potential recruits may result in speedier recruitment thereby reducing time taken to complete the study. This is of particular importance if companies are competing against each other to get a similar drug to market. The first company to gain a licence to sell the new medication will have a real financial advantage over their competitors. The development cost of conducting clinical trials in the developing world is also lower than in the West due to cheaper infrastructure costs, including lower staff salaries and overheads. Some would argue that trial standards are also less stringent than are required in the West, making it easier both to recruit and complete trials in a timely manner. Taking these factors into consideration, why would pharmaceutical companies then choose to conduct clinical trials in the West? There are a number of reasons. Firstly, while the numbers may be small the potential participants will have been closely monitored enabling researchers to have robust baseline characteristics.

This may not be the case in LEDCs where CD4 count and viral load monitoring is not routine. Secondly, research will be conducted in centres which have an established research track record supported by experts in the field. These centres also have access to laboratories and processes in place to ensure that samples are dealt with as per protocol. Protocols are also in place to ensure that clinical trials are closely monitored and deviation from these protocols or safety concerns are reported swiftly, thereby ensuring that the data which is collected can be validated. Finally, and more importantly, the ethical standards for conducting trials in the UK are stringent ensuring that participants are protected from harm.

While the number of participants may be small, the results from HIV trials based in the UK add enormously to our understanding of HIV and to the development of new classes of antiretroviral therapy.

Types of clinical trials

Clinical trials of new medications are generally sponsored by the pharmaceutical industry. It may take around twelve years from commencing development on a new drug until it is given a license for use on patients. The International Conference on Harmonisation of Technical requirements for Registration of Pharmaceuticals for Human Use (ICH) (CPMP/ICH/286/95, 2000) recommends that all medications for human use must first be tested on animals. If the safety profile is acceptable, the medication may go on to be tested in humans. However, in order to begin trials on humans, the drug must first be certified by a national licensing authority. In the UK,

this is the Medicines Control Agency or the European Medicines Evaluation Agency. Only when this approval has been granted can the company begin clinical trials to establish its efficacy, safety profile and dosing levels. If the study medication fails to meet the safety or efficacy criteria at any time, development will cease. For every new medication which is successful in gaining a license, many hundreds will be rejected. The cost of developing a new drug varies. However, the standard cost from inception to licensing is in excess of \$800 million (GlaxoSmithKline, 2011). The new medication will only have a patent for twenty years, during which time the pharmaceutical company will try to recoup its developmental costs.

There are different types of clinical trials. The first of these, Phase One trials, are designed to test the safety of a drug on healthy volunteers and the effects of the medication on the body. As this type of clinical trial looks at the first use of the medication in humans they carry more risk to the participants. Most Phase One trials in the UK are conducted by contracted research organisations. As Phase One trials are designed to test the safety of a new medication, companies have to take great care to safeguard the well-being of volunteers. Medication is titrated, starting below the safe level of dosage given to animals. Volunteers are kept under close observation to ensure that any unexpected side-effects are dealt with. This type of trial also looks at how quickly the medication is absorbed and how long it remains active in the body. Phase One trials test new medications against placebo drugs in order to check their efficacy. Volunteers are randomly assigned to either arm, and are 'blind' to what treatment they are receiving. This is done by trying to ensure that both

the placebo and the new medication are similar in appearance and are given by the same method. i.e. both are given orally or intravenously. Phase One trials tend to take two years to complete. However, individual volunteer participation is generally only for a few weeks (Quintiles, 2010).

There are some ethical considerations specific to Phase One trials. These trials depend on the use of volunteers, many of whom are students or those on a gap year between school and university. The volunteers are generally fit, not on any medication, free to commit the time needed to participate and compliant to the needs of the trial. As such, they are perfect Phase One research participants. However, some concerns have been raised regarding the payment of volunteers. The level of payment was set by the ABPI (ABPI, 1988) and the RCP (RCP 1986). These guidelines state that payments must not be so generous as to influence participation. The level of payment must also take into account the length of residence in the research facility, level of discomfort, number of visits and inconvenience. While it is accepted that volunteers should get paid for these aspects of participation, they do not receive payment for risk. This is inconsistent with other walks of life where risk taking is compensated. For example, commercial divers get paid for the risk they take in addition to their role. Phase One trials are classed as non-therapeutic research. As such, it is not expected that those volunteering will gain any health benefits from participation. Any health benefits which they do gain are incidental to the aim of the study. While no benefit is anticipated, this type of trial may carry some risk to the individual as the study medication has not been previously used in humans. Animal

studies do give some indication of which side effects may be expected. However, no matter how good these trials are, human physiology is very different from that of animals. This was demonstrated recently at the Phase One clinical trials unit at Northwick Park Hospital, where a new monoclonal antibody (TGN1412) for the treatment of rheumatoid arthritis was tested on humans for the first time. Animal studies had found no safety concerns. However, the antibody response on the human subjects led to serious organ failure (Moberly 2007 p.342).

In order to reduce the risk from participation in phase one trials, ABPI guidelines (ABPI 2007) suggest that volunteers must leave a period of four months between participating in clinical trials. This period can be extended if the volunteer had been involved in a clinical trial of a biological agent, which may take longer to 'clear' from the body. Other organisations such as the RCP and the EU GCP offer no guidance on the length of time between trials. Volunteers who participate in these trials often do so for financial benefits. When enrolled in a Phase One trial, volunteers stay in the research facility where their accommodation and food is free. Combined with the fee for participating, some individuals find it very tempting to try to enrol in 'back to back' trials. In order to help alleviate this problem, a voluntary register called 'The Over-Volunteering Prevention System' (TOPS) was set up by centres conducting phase one trials (Boyce 2003, p.418). Participants are asked to produce either a passport or a national insurance number and are photographed. Participating centres can then check to see if the volunteer has waited the requisite time between trials. While this scheme is voluntary, twenty-eight out of thirty-one units which conduct Phase One

clinical trials in the UK subscribe to it. (Personal communication with Malcolm Boyce, May 2008). This helps to regulate the participation in trials and helps to safeguard the well-being of participants.

In Phase Two trials, the drug is used for the first time in patients who have the condition the medication is designed to benefit. The trial is designed to test the efficacy of the medication on patients, look at short-term safety, establish the optimum dose of the drug and establish if it causes any side-effects. Phase Two trials are generally placebo controlled, as this is required by some licensing authorities such as the Federal Drug Agency in America (Code of Federal regulations Title 21, 2011). Some patients will receive the active medication, while others will receive an active substance which looks identical to the trial drug. Placebos are used to check if the effects of the new medication are real and not imagined. People often report that they feel better having had a drug when in effect they have received an inactive substance. The use of a placebo also helps to overcome bias in reporting the effects of the new medication. The Declaration of Helsinki (1996) article 2.3 recognises that:

In any medical study, every patient - including those in a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

Despite this, there are some concerns around the use of placebos in clinical trials.

The first of these is ensuring that the patient is fully aware that they might not be on active treatment for the duration of the study. This information should be clearly outlined in the participant information sheet (PIS) and during the consent process. I will discuss the ethical issues of PIS in chapter 6. The second consideration is the potential risk to the patient from treatment being withheld during the trial period. This is not such a concern for trials investigating a condition which may have no proven standard treatment. However, in some other trials withdrawal of medication may involve some level of discomfort for the patient. Clinical trial protocols generally allow rescue medication which can be used to alleviate any symptoms the patient may experience as a result of withholding treatment. When ethics committees review trial protocols, they ensure that there is some means of identifying any medical deterioration as soon as possible, withdrawing the patient from the trial should this occur. An alternative to placebo controlled trials is to compare the new medication against standard treatment. This is not always possible where the licensing authority demands a placebo controlled trial to prove the efficacy of a new medication when there is already an established medication for the condition on the market. This demand conflicts with the Declaration of Helsinki (2000), which suggested that placebos should only be allowed in a clinical trial where there was no recognised treatment for the condition under investigation. Drug companies respond to this by countering that the standard treatment in use for some time may never have been subject to such stringent testing. In order to address the confusion over the interpretation of the existing guidelines, The World Medical Association (WMA) (2001) issued a note of clarification on the use of placebos in clinical trials. It reiterated that

the use of placebos was not acceptable where there was already an established treatment for the condition being investigated. Placebos could be used where there were 'compelling and scientifically sound methodological reasons the use of placebo controlled trials are necessary to determine the safety and efficacy of drugs' (Human, 2001). Human gave an example of the use of placebos in a clinical trial investigating the treatment of baldness or allergic rhinitis where the participant would be at no additional risk for the use of a placebo. Placebos were also acceptable in clinical trials where patients were not denied standard therapy. In HIV clinical trials the use of placebos is generally not permitted, as antiretrovirals are the 'gold standard' of treatment. However, placebos may be used as part of the background therapy, where the trial participant will still be receiving the gold standard treatment in addition to the study medication.

If the Phase Two trial has demonstrated that the drug is beneficial to patients and the side effect profile is acceptable, it will go on to a Phase Three trial. Phase Three trials are also conducted on patients who have the condition the study medication is designed to treat. These trials are designed to look at long-term efficacy and safety in order to gain a license to market the drug. Phase three trials recruit greater numbers of research subjects, and participation is much longer. Phase Three trials generally compare the new drug with an existing drug in an attempt to demonstrate its superiority. Patients are randomised to different groups, one group will receive the new treatment, and others will receive the standard treatment. The comparator drug is one which is the 'gold standard' treatment for the condition which is being

investigated. Phase Three trials may also involve a third group of patients which are given a placebo. However, the investigators have to demonstrate to the ethics committee that procedures are in place to ensure that patients who are in the placebo group will not be adversely affected by lack of treatment. Both patients and investigators are not aware which group the patient is in to remove possible bias.

If the clinical trial has found the study medication to be efficacious and safe, the pharmaceutical company may make it available on a compassionate basis to individuals who participated in the trial prior to the medication being granted a licence. Continuing a study medication on this basis is usually only permitted if there is no other treatment available for the condition, and the participant has responded to the treatment. The participant will continue to be followed up by the company until such times as the medication is licensed. The compassionate use of study medication has been available to some HIV positive individuals who had developed drug resistance and were found to have had a good response to the new treatment.

Once a drug has been granted a licence, the pharmaceutical company may choose to conduct a Phase Four trial. This type of trial is again conducted on patients and is designed to look at the continued efficacy of the drug, long-term side-effects and any advantage the new medication may have over other drugs licensed for this indication. Phase Four trials may also look at alternate dosing of the drug, for example, giving it once a day instead of twice daily. It may also look at why some patients do not respond to the drug.

Submitting an application for ethical approval

The clinical trials legislation requires that clinical trials in medicinal products (CTIMPS) be reviewed by RECs that are legally recognised by the United Kingdom Ethics Committees Authority, (UKECA). The process of submitting an application to the ethics committee for a clinical trial relating to a medicinal product is outlined in the Standard Operating Procedures (SOPs) for the Research Ethics Committees (UKECA 2007). These SOPs meet the obligations of the UK Government under directive 2001/20/EC of the European Parliament and the Council of the European Union for the operation of ethics committees in relation to Clinical Trials of Investigational Medicinal Products.

The application for ethical review is submitted by the chief investigator (CI). It is then placed on the data base and given a unique REC number. The NRES central allocation system allocates applications for Phase Two and Phase Three trials to the appropriate committee. Applications and supporting documentation must be submitted within four days of booking an application, which in turn must be submitted both electronically and on paper with signatures. The REC co-ordinator then has five days to validate the application and respond to the CI. The ethics committee then has a sixty day period after validation of the application to give ethical approval. If the REC requires further information before confirming its opinion it can make one request only for that information during which time the sixty day clock will stop. Ethical opinion can only be given following a REC meeting.

Each committee meets monthly, with at least ten meetings per annum. The meeting requires a quorum of seven members, including chair or vice chair, one lay and one expert member. The role of the ethics committee is to review the research protocol to ensure that the proposed research will not harm the individual, the researcher or the name of the institute where the research is being conducted. Prior to the committee meeting each protocol is allocated to two lead reviewers who will report back on their findings to the main committee. In order to help them reach a decision, the reviewers will take into consideration the suitability of the applicant. Are they experienced in the type of research they are planning to undertake? Who will be conducting any tests? They will look at the design of the study, to see if it can meet its objectives and where the study is to be conducted. If it is planned to conduct research in the community, the reviewers will want to ensure that the safety and well-being of individual researchers has been considered. The reviewers will look at any risks or burdens of the research such as number of visits and type of procedures participants will be expected to undergo. They will look at the participant information sheet to see that it truly reflects what is written in the protocol and that it is written in a format which will be understood by the proposed research population. The reviewers will also check that measures are in place to protect the confidentiality of participants, as well as indemnity and compensation should the individual come to any trial related harm.

The main reviewers will give a brief overview of the protocol and any ethical concerns they have about the study to the main committee. This will be followed by comments

from other committee members. The researcher will then be asked into the meeting room to discuss the main issues. Following their departure, the committee will discuss the protocol in more detail before reaching a decision. The CI is informed of the committee's decision within ten working days of the meeting. The committee can give the application a final opinion (favourable or unfavourable), or a provisional opinion with request for further information or no opinion (if it is waiting for comments from a referee). Should the decision be unfavourable, the applicant can appeal the decision of the first REC. They also have the option of re-submitting the application to another REC for their opinion. Before commencing a clinical trial in medicinal products the sponsor must obtain clinical trial authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA 2008).

Phase One trials are dealt with by specialist ethics committees. Prior to the inception of COREC, protocols for Phase One trials had been reviewed by the pharmaceutical companies and contracted research organisations. However, the Association of British Pharmaceutical Industries (ABPI) recognised that these committees should be seen to be unbiased in their reviews. They produced guidelines in 1988 to aid those conducting phase one trials (ABPI 1988). The requirement for ethical review for phase one trials changed in 2001, when they were incorporated into the EU Clinical Trials Directive (2001/20/EC). Under these changes, phase one trials are now reviewed by independent research ethics committees accredited by the UKECA. The ABPI guidelines were updated in 2007 (ABPI, 2007) to reflect the changes to clinical trials regulations.

Summary

This chapter has briefly outlined the background to clinical trials and the procedure for gaining ethical approval. Clinical trials are necessary to further our understanding of disease and to ensure that new medication is safe and effective. In the past, patients were often enrolled into clinical trials without consent, and given little information about the purpose and reason for the trial. Following the Nuremberg trials, guidelines were issued outlining principles which ensured that the safety and well-being of participants were placed above the success of the clinical trial. These guidelines have legal standing in most countries, offering research subjects protection against harm and compensation should harm occur.

I have looked at some of the reasons why the development of new HIV medication is needed. On a global level, HIV has already begun to have a negative effect on the world economy. Without the development of more cost effective antiretrovirals which have a better resistance profile, HIV will continue to adversely affect the health and well-being of those living with the virus. This in turn will affect their ability to work. As the prevalence of HIV increases, the detrimental effects of the virus will continue to have a devastating effect on the economy of developing countries which have the greatest need for growth. Clinical trials enable researchers to test the efficacy, safety and tolerability of antiretroviral medications. While the number of potential trial participants living in the UK is small in comparison with other global areas, there is still a place for HIV related clinical trials to be conducted in the UK. The knowledge

gained from UK based trials is crucial to improving our understanding of HIV and the development of innovative new treatments. In this chapter I have briefly touched on the role of the research ethics committee. I propose to discuss in depth their role in protecting participants from harm in later chapters.

Chapter 4

How antiretrovirals work

Once infected with HIV, the virus can be detected in the blood. The level of the virus can range from undetectable to over a million copies/ml, and is measured by taking a viral load test. The virus destroys the cells of the immune system, reducing the individual's capability to fight infection. The British National Formulary (2011) reports that there are twenty-two HIV drugs licensed for use in the UK each attacking HIV in a different way. There are five main classes of antiretrovirals, with more being developed. The oldest classes of HIV drugs, the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), stop HIV from replicating within cells by inhibiting the reverse transcriptase protein. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are another of the older class of antiretroviral drugs which stops HIV replicating within cells by interfering with HIV's reverse transcriptase protein, which it needs to make new copies of itself. The protease inhibitors target the HIV protein to stop the production of new HIV. The fusion inhibitors are a new class of HIV drug which targets the point where the virus locks itself to proteins on the cell's surface. The other new class of drug is the integrase inhibitor, which stops HIV from inserting its DNA into the host cell.

First line therapy usually involves giving two drugs from the NRTI class and one from the NNRTI class (BHIVA, 2009). However, due to the composition of the drugs, individuals may only need to take a couple of tablets twice a day. Some of the antiretroviral drugs, such as Trizivir, comprises of two or more medications given in

the one tablet. If an individual becomes resistant to this regimen, they will be switched to second or third line regimens, comprising of drugs from the other classes of drug. This will be informed by the results of an HIV resistance test. Second and third line regimens are often more difficult for the individual to take as they may include upward of six tablets twice daily, possibly with the addition of injected drugs. Due to the increased number of drugs, the individual will be at increased risk of developing side effects.

Why new treatments are needed

Despite the number of antiretrovirals available on the market, there is a need for new medications to be developed. It is very common for people to experience side effects to antiretroviral medication. These side effects include headache, nausea and diarrhoea, which can be easily treated. However, some medication can lead to the development of more serious side effects, such as diabetes and abnormal liver function. Malvestutto (2010) has also reported on an increased level of heart disease in individuals who have been taking antiretrovirals for a number of years. The development of antiretrovirals with a better side effect profile will greatly improve the health of people living with HIV, increase their overall prognosis and reduce the number of clinic visits and inpatient stays.

Possibly the greatest threat to the well-being of HIV positive individuals are the development of antiretroviral resistant strains. HIV is a highly variable virus which mutates easily; this is one of the reasons why it has been so difficult to develop

effective treatment. Cross resistance is also common, where resistance to one drug in a class will result in some degree of resistance to all the other drugs in that class. While resistance can develop when medication is not taken correctly, Carter (2007) has also shown conclusive evidence for the transmission of drug resistant strains of the virus. This has led to BHIVA (2011) recommending that all newly diagnosed individuals have a HIV resistance test prior to initiating antiretroviral therapy. Initiating treatment for those found to have a drug resistant strain of the virus can be more challenging, as their choices of treatment will be more limited. Wittkop et al (2010) showed that individuals who had a resistant strain of HIV often need to be commenced on a regimen consisting of a number of tablets, which in itself can lead to poor adherence and the development of further drug resistance. Further studies are planned to establish if the long term prognosis for these individuals is worse than individuals with drug sensitive strains of the virus.

Why recruit HIV positive individuals from LEDCs?

In order to test the resistance profile of a new HIV medication, it is desirable to recruit participants who have no HIV mutations. These individuals have what is known as 'wild type' virus, and are likely to have had no previous exposure to antiretroviral medication. As discussed in chapter 3, while access to HIV testing is becoming easier in LEDC's, access to treatment remains problematic. Even if available the cost is often prohibitive. As such, many of those who contract HIV in LEDCs will have no prior exposure to antiretroviral medication and will have less opportunity to develop antiretroviral resistant strains of the virus. This is - in part - due to the lack of

availability of antiretroviral medication in their country of origin. The HPA (2010) supports this, reporting that newly diagnosed individuals who originate from sub-Saharan African are less likely to have acquired a resistant strain of the virus, and therefore have less viral mutations. In addition, many will be unaware of their HIV status prior to arriving in Britain and being offered HIV testing.

The easiest way to measure a response to medication is to initiate treatment in someone with a high viral load and low CD4 count. They are closely monitored, taking into consideration how long it takes for virus to respond to treatment, any potential side effects and ease of administration. The higher the viral load, the easier it is to monitor response to treatment (BHIVA, 2005). The Health Protection Agency (2010) reported that newly diagnosed individuals who originate from sub-Saharan African tend to present late, having acquired HIV long before they test. Thirty-five percent of heterosexual women and forty-two percent of heterosexual men were found to have a CD4 count of less than two hundred per mm within three months of diagnosis. With this level of immune suppression they are at serious risk of opportunistic infection. Of the five hundred and sixteen people who died of HIV in 2009, seventy-three percent had presented with a low CD4 count. As such, newly diagnosed individuals from sub-Saharan Africa are more likely to have a higher viral load and lower CD4 count than those who have contracted HIV in the UK and are diagnosed earlier in their infection.

How many asylum seekers and refugees from LECDs are HIV positive? The truth is, we just don't know. In the absence of any official data, Gazzard (2005) estimated that

twenty percent of new those newly diagnosed with HIV in the UK were asylum seekers or refugees. These figures arrived at using data immigration data and HIV prevalence data. While this data may be a starting point, it does not take into consideration the prevalence rates in the specific countries. For example, while we have robust data of HIV prevalence in Uganda due to local initiatives, countries such as Sudan do not collect this information. As such, these figures may underestimate the true extent of the problem.

Physicians may be unaware of the immigration status of patients under their care. HIV testing is usually conducted in sexual health clinics (SHC). Under the NHS Trusts and Primary Care Trusts (Sexually Transmitted Diseases) Directions 2000, individuals attending a SHC are not obliged to give their correct name, address, date of birth or ethnicity. The immigration status of individuals is not required; treatment for sexually transmitted infections (STI's) is free to all under the National Health Services (Charges to Overseas Visitors) Regulations (2011). In hospitals where HIV care and STI care are combined, it is possible for patients to continue using an assumed name and details for some time, and never be asked their immigration status. In other hospitals, treatment of STIs and HIV are quite distinct. If an individual is found to be HIV positive in the SHC, they will be transferred to the HIV clinic where their details and immigration status will be ascertained before commencing treatment. Until there is a robust method of record keeping, and what that system might look like, it will remain impossible to have a true number of HIV asylum seekers and refugees.

The HPA (2010) found that the majority of those testing positive from sub-Saharan Africa had not had a previous HIV test prior to coming to the UK. There may be a number of reasons for this. For some people, there would not be any benefit to finding out that they were HIV positive if they could not access treatment. For others, testing seemed unnecessary. As one of my patients explained; 'My husband had died of HIV, my child had died of HIV, and I knew that I must have it'. For some fleeing oppressive regimes, health care - including HIV testing - is very low on their priorities. Once they have arrived in Britain they can choose to take advantage of a number of initiatives designed to increase testing within the African community. While these have had some success, there are still barriers to testing. Of these, confidentiality appears to be the greatest concern. Individuals are concerned that should they test positive, their community in the UK will be informed and the news will reach their family back home. Despite anti-discriminatory legislation, HIV remains a stigmatising infection. Patients have reported being removed from GP lists and refused dental care once their status has been revealed. If this reaction is seen from health care workers, it is little wonder that individuals decline to test despite being informed of the health benefits of testing and potential risks from not knowing your HIV status.

Why not recruit other HIV positive populations to trials?

Would it be possible to conduct HIV trials in the UK without asylum seekers and refugees? The answer to that question depends on the type of trial. Let us start by looking at the types of HIV trials conducted in the UK. There are three main types: observation trials, vaccine trials and drug trials. In observation trials individuals are

followed up for a period of time. This type of trial does not involve any changes to medication. Vaccine trials recruit both HIV negative and positive individuals, some looking at ways of preventing transmission, others looking at stopping viral replication in the positive person. Drug trials involve the development of new classes of medication as well as studying the efficacy of new combination therapy. While HIV positive asylum seekers would be able to enrol in observation and the vaccine trial provided they fulfilled the study criteria, it is in drug trials that they are most valuable. Their lack of exposure to antiretrovirals coupled with a low CD4 count and high viral load make them particularly attractive to researchers. Asylum seekers and refugees who have developed drug resistance would also be eligible for trials on second and third line drugs. Of the 65,319 individuals living with HIV in the UK, the HPA (2010) reported that fifty-one percent (33,310) of those were heterosexual, of whom sixty-six percent were black African. Of the remaining thirty-four percent the majority were men who have sex with men (MSM), with a small proportion infected through injecting drug use and mother to child transmission. Despite the seemingly large pool of potential recruits, researchers can find it difficult to find the number of participants required to show significance in a trial. This is in part due to the eligibility criterion of different trials. For example, trials on new drugs may only want to recruit participants who are antiretroviral naïve. These criteria are more likely to be found in individuals from sub-Saharan Africa who have not been exposed to antiretrovirals, than UK born individuals. If we look at the HPA figures, it would appear that the majority of individuals living with HIV in the UK are from sub-Saharan Africa. However, the figures include those who have been in the UK for a number of years. These

individuals may have been exposed to drug resistant strains of the virus in the UK, making them ineligible for trials of new drugs. There is also the probability that as the availability of antiretroviral drugs increases in Africa we will begin to see the emergence of resistant strains of the virus. In time, the number of individuals with wild type virus will decrease. For the moment, HIV positive individuals from sub-Saharan Africa are more likely to have wild type viruses than their UK born counterparts and so are valuable in drug research.

Clinical trials also require that individuals have a break between trials, to protect both their health and the integrity of the trial. Some of the larger centres can be involved in a several trials simultaneously. In these, individuals may have participated in several trials over the years and may not always want to enrol in another one, especially if it requires multiple clinic visits and changes to life style. This will also reduce the 'pool' of individuals who may be eligible to participate. We must also remember that some HIV positive individuals, like individuals with other chronic health conditions, may just want to get on with their lives and not participate in trials. Taking into consideration the number of HIV positive people in the UK and the number of HIV trials, it would be difficult, if not impossible to conduct HIV trials in the UK without recruiting HIV positive asylum seekers and refugees.

Summary

HIV positive asylum seekers and refugees from sub-Saharan Africa are less likely to have been exposed to antiretrovirals than UK born positive people. As such, they are

more likely to have wild type virus which is valuable when testing the response of new antiretroviral medication. In addition, they are more likely to present at clinics with a high viral load and low CD4 count, which allows researchers to more accurately measure the response to treatment.

Due to the number of HIV trials being conducted in the UK - and the eligibility criteria of these trials - it would be difficult to see how HIV clinical trials could run without the participation of HIV positive asylum seekers and refugees.

Chapter 5

Participating in clinical trials carries both risks and benefits. The extent of these risks and benefits depends very much on the type of trial. For example, someone participating in a Phase Four to establish a new indication for a licensed drug may be at considerably less risk than an individual who is participating in a Phase Two which is seeking to develop a new cancer drug. In the former, the drug will already have undergone safety trials while in the latter the side effect profile will have yet to be established. In this chapter I will focus on the specific harms and benefits HIV positive asylum seekers and refugees may be exposed to as a result of participating in HIV clinical trials. I will look at the responsibilities to prevent harm in this group and outline measures which would reduce these harms.

What is harm?

Beauchamp and Childress (2011) p115 define harm as thwarting, defeating or setting back some parties interest. This is based on their principal of non- maleficence, where one ought not to inflict evil or harm. HIV positive asylum seekers and refugees may experience harm as a result of participating in a clinical trial. I will begin with the potential to develop drug resistance as a result of dispersal. As discussed in Chapter 3, HIV drug resistance can occur for a number of reasons, including failure to take HAART as prescribed. BHIVA (2001) reports that the virus is able to mutate if the level of antiretrovirals in the blood drops below a specific level. Patients are advised that if they are planning to stop treatment, they should first discuss it with their physician. Due to the different half-lives of antiretrovirals, abrupt cessation is likely to

lead to a resistant strain of the virus developing. All people taking HAART have a risk of developing drug resistance if the compliance rate falls below ninety-five percent. While the general HIV population have control over their drug compliance, this may not be the case for HIV positive asylum seekers and refugees.

Development of drug resistance

The UK Border Agency is able to disperse asylum seekers and refugees to other regions of the UK areas with little notice. BHIVA (2009) has raised concerns that asylum seekers who have been dispersed do not have time to contact their clinics to arrange transfer to another unit - leading to breaks in their treatment. Others have had HAART taken into 'safe keeping' on their journey, and have never seen it again. In the clinic where I work, several clinical trial participants have been dispersed or deported with little heed taken of their medical needs. Clinics are seldom told by the authorities that the individual has been dispersed; information about their whereabouts usually comes via refugee or local HIV organisations. If dispersed within the UK, they may be placed in areas where there is no local HIV service. Burnett (2010) reported that some asylum seekers find it difficult to access another centre due to language difficulties. Access can also be hindered while they try to establish that they have a legitimate right to medication. This is especially problematic for those asylum seekers and refugees who are no longer eligible for treatment and are accessing drugs via a clinical trial. It is unlikely that the authorities would allow them to continue participating in the trial, as this would mean arranging escorts and transport to clinic. They may not have sufficient medication to enable them to stop

HAART in a structured manner, potentially leading to the development of drug resistance.

Stevenson (2012) expressed concerns about the treatment and care of HIV positive individuals who were detained prior to deportation. It is difficult to establish exact numbers of those affected as the HIV status of detainees is not recorded. However, Inegbenebor (2012) reported that individual detained in Immigration Removal Centres were experiencing interruptions to their treatment. Staff may have little HIV knowledge and be unaware of the risks of withholding or delaying HAART.

Those who are deported may also be at increased risk of developing drug resistance. Stevenson (2012) reported that individuals who are deported are usually given very little notice and may not have been able to safely stop HAART. While global access to HAART has increased over the years, UNAIDS (2009) reported that only thirty-one percent of people in low to middle income countries were able to access treatment. This situation has deteriorated in recent months due to the economic debt crisis in Europe. Collins (2012) reported that suspension of round 11 of the Global Fund Grants has meant that countries who have previously had limited funding for HIV treatment have had their funding suspended. If treatment is available, it is very unlikely that the antiretrovirals which constitute the clinical trial HAART regime would be available. Indeed, in some LECDs only dual therapy is available. If available, they will still be under patent and will be more expensive than the generically produced ARVs. Treatment of resistant strains of the virus can be a challenge and will require

the addition of new classes of ARVs or novel combinations of drugs. Chatora (2010) states that the cost of second line treatment, used in drug resistance, was five times more expensive than standard treatment. This will place an ever greater burden on those with limited funds. Due to the development of cross resistance between different classes of antiretrovirals, individuals could have already developed resistance to the medications available in their home country. As such, the available treatment would be unlikely to be fully effective. In the West, all patients are encouraged to have a resistance test prior to commencing treatment or changing antiretroviral therapy. This enables clinicians to choose drugs which will be effective. Price (2011) expressed concerns about the lack of ARV resistance testing in East and Southern Africa. Their study showed that while resistance levels were rising, availability to resistance testing was available to very few. Resistance testing is of particular value in choosing treatment regimens for individuals who have been at risk including participants in clinical trials who have stopped treatment abruptly. Lack of effective treatment can lead to rapid viral rebound. Over a short period of time the immune system will fail, leading to the development of opportunistic infections and death.

Should asylum seekers and refugees be permitted to participate in HIV clinical trials where they face an increased risk of development of drug resistance? I suggest that the benefits of participation outweigh any harm. Asylum seekers and refugees may be at a greater risk of developing drug resistance due to the possibility that they will be dispersed or detained, leading to abrupt withdrawal of medication. Even if they are

aware of the risks, they may find it impossible to structure withdrawal if they are not permitted to access medication.

However, many of these individuals may not be able to access antiretroviral therapy at all if they were not participating in a clinical trial. Harrigan (1999) found that those stopping HAART experienced a rebound in viral load and drop in CD4 count leading to the development of opportunistic infections and death. In contrast, those who remained on therapy had a much better long term prognosis. By continuing to access treatment via the clinical trial, the individual may be giving themselves the best possible chance for future good health. Some might suggest that this is just delaying the inevitable, as the individual may not have access to effective medication in their country of origin. This is certainly true. However, the deportation process can be very long and the outcome is by no means certain. The Home Affairs Committee (2012) found that forty percent of those awaiting a decision on asylum had been permitted to remain in the UK. While this may be more a reflection on the inefficiency of the UK Border Agency, it does give those in the process of seeking asylum hope. Accessing antiretroviral therapy via a clinical trial may not be ideal. Despite being fully informed of the risks of developing drug resistance and the detrimental effect this will have on their health, those in need of treatment may not feel that they have any other choice if they wish to remain well.

Potential harm to others

The development of drug resistant strains of the virus can also affect sexual partners.

The overall risk of contracting HIV from a single episode of unprotected sex with an HIV positive individual is one in three hundred. Transmission is dependent upon many factors such as the viral load of the infected person - if they are on treatment, the sub-type of the virus and if they or their partner have another sexually transmitted infection. If a condom is used correctly, the risk of contracting HIV can be greatly reduced. Those infected with a resistance strain of HIV have a poorer outcome than those who contract a non-resistant strain. Steingrover (2008) found that the treatment options with those that had the transmitted resistant strains were reduced and they had an increased risk of developing an HIV related illness. This is even more problematic in LEDCs where treatment options are limited. In LEDCs background health problems also increase the of HIV transmission. Malnutrition - which is common in LEDCs -lowers the immune system and increases the possibility of transmission. Ulcerating genital infections - such as chancroid - increase HIV transmission and are more common in LECDs. In the West, pre-exposure HIV prophylaxis (PREPSI) is available, which, when taken prior to sexual exposure, significantly reduces transmission. A short course of ARVs given to the HIV negative partner within seventy-two hours of unprotected sexual intercourse (PEPSE) offers a seventy-five percent reduction in onward transmission of the virus (Expert Advisory Group on AIDS, 2004). Despite this treatment being unlicensed, it is recommended by the British Association on Sexual Health and HIV (BASHH) (2006) and is accessible from accident and emergency departments and sexual health clinics. These options are seldom available to those at risk of transmission in LECDs.

HIV positive individuals may find it difficult to disclose their status to sexual partners potentially exposing them to resistant strains of the virus and the associated health risks. There still remains a significant level of stigma surrounding HIV. Disclosure exposes the individual to the reactions of others - possibly rejection and in some cases violence. An additional barrier to disclosure for individuals who have tested positive while in a sexual relationship may be fear of legal prosecution. Nyambe (2005) reported that in thirty-six out of forty-one European countries, HIV transmission is a criminal offence. In England and Wales, thirteen people were prosecuted between 2003 and 2008. All of these individuals were convicted of Reckless Transmission of Infection under Section 20 of the Offences Against the Person Act 1861. (Dica, R. v R (2004) EWCA crim 1103, Konzani, F. V R (2005) EWCA crim 706). Ten of the defendants were convicted, all receiving custodial sentences; three were acquitted. In addition, a large number of accusations have been made but have never reached the Crown Court (Crown Prosecution Service, 2008). The process of taking such a case to court can be intrusive and distressing for both the accused and the accuser as the sexual history of both parties will be investigated in detail and used in court. While this legislation was intended to reduce intended transmission of the virus, THT (2010) has expressed concern that it may deter individuals who have been at risk from testing. It has added to the stigma of HIV and may have the opposite effect of hindering disclosure.

In order to avoid disclosure, some HIV positive individuals choose to use a condom to protect their partner from infection. While this is certainly better than using no

protection, condoms are not a hundred percent effective as proved by the number of unintended pregnancies each year. Nor does it enable them to take advantage of PEPSE if the condom were to split.

While the HIV positive individual may be concerned about the reaction of others, the difficulties in disclosure do not override their duty to those whom are at risk from sexual transmission. Erin and Harris (2002) suggest that HIV positive individuals have a strong moral duty to disclose their status to intended partners. If the intended sexual partner is unaware of their partners HIV status and the potential risk of transmission, they cannot make an informed choice about whether to have sex with them. They suggest that once the HIV positive individual has informed their sexual partner they have discharged their moral obligation. The decision to have sex and potentially risk contracting HIV is left to the HIV negative individual. However, this stance does not take into consideration other factors. The sexual partner may not have a great understanding of HIV, or be aware of the risks of contracting it through unprotected sexual intercourse. Bluthenthal (2012) found that despite health promotion campaigns, a number of people still believe that HIV can only be contracted through injecting drug use or homosexual sex. For these individuals, having knowledge of their partner's status may not alert them to any potential risks. The HIV negative partner may also be at risk in relationships where there is a power imbalance. They may be financially or emotionally reliant on their partner. Even if the HIV positive partner were to disclose their status, they may feel powerless to instigate safe sex. Smith (1997) found that for some HIV negative individuals, emotional attachment to

their HIV positive partner may negatively influence their ability to protect themselves from harm. They may feel that having sex with their partner demonstrates that they care and are willing to share risks.

Those HIV positive individuals who are receiving HAART may have a greater obligation to inform sexual partners as they will be aware of the benefits of treatment. This is particularly true of asylum seekers and refugees who have sought out clinical trials as a means on continuing HAART. Informing sexual partners will enable them to access treatment and the associated health benefits. It could be argued that those who are on stable treatment with an undetectable viral load are significantly less likely to transmit HIV sexually and therefore may not have as great an obligation to inform sexual partners. However, serum blood viral loads do not always correlate with the levels of virus present in semen or vaginal secretions. This also may not be the case for individuals who have developed a drug resistant strain of the virus. The sexual partners of these individuals have a greater risk as their treatment options are significantly reduced.

Bennett et al (2000) suggest that the individual has a moral duty to disclose only if there is a significant risk of infection. This may be problematic in a sexual context. The HIV positive individual may have chosen not to inform their sexual partner, planning only to have 'low risk' sexual activity with their partner. During this activity, what begins at 'low risk' may escalate to 'high risk'.

Protection against sexual transmission of HIV should be a shared responsibility. For those HIV negative individual who can understand the risks of contracting the virus and are not under undue pressure to have sex, being told their partners status enables them to make an informed choice. However, HIV positive individual should be aware that not all their partners will understand the risks of sexual transmission, while others may choose to ignore these risks.

Harm caused by dispersal and deportation on the scientific validity of the trial

During the development of trial protocols, statisticians calculate the number of participants needed to show statistical significance. As part of these calculations, they allow for a number of participants to leave without completing the trial. If the number of participants lost is greater than envisaged, the trial may be underpowered and unable to reach a meaningful conclusion. Casciani (2011) reported that The Immigration Authorities are under increasing pressure to clear the backlog of failed asylum seekers and refugees. While there is a long delay between being refused asylum and being deported, researchers who are planning to recruit from this population, but will need to take into consideration the possibility that some participants may be dispersed.

The abrupt withdrawal of asylum seekers and refugees may also affect the safety profile of the trial. During each study visit, participants will have tests taken to see if the medication is causing any systemic changes in the body. As HIV drugs can remain in the body for some time, side-effects may not show immediately. If

dispersed or deported, any adverse effects could be unreported and not available when writing the safety profile of the new medication.

Multiple-participation in clinical trials

Boyce (2008) defines multiple-participation as ‘individuals participating in more than one trial without the knowledge of their clinician’. This practice can affect both the well-being of the individual and the scientific validity of the study. There are many reasons why individuals enrol in more than one clinical trial. Phase One trials attract students or those on a gap year. Volunteers in these trials are paid for participation, in addition to having free food and accommodation for the duration of the trial, albeit in a research facility. For participants in this type of trial, additional financial reward is likely to be the reason for multiple-participation. While Phase Two to Four HIV clinical trials do not offer financial incentives to volunteers, HIV positive asylum seekers and refugees may benefit from multiple-participation in other ways.

Multiple-participation enables individuals to stock-pile HAART which will enable them to continue treatment if they are dispersed or deported. For the participants who are supporting families in their country of origin, excess HAART can be sold and the proceeds sent home to purchase basic commodities such as food and fuel. For others, multiple-participation will enable them to send home HAART to family members who are also HIV positive but are not able to access treatment.

When study protocols are developed, researchers ensure that trial participants are

not burdened by too many investigations and that the number of tests does not exceed safe limits. Volunteers participating in multiple trials will be exposed to more tests they would undertake in a standard clinical trial. For example, participants may be required to have x-rays as part of the trial protocol. The safe level of radiation is calculated based on the number of tests each individual requires. If participants are required to have x-rays in additional trials, they will be exposed to much higher levels of radiation, which can lead to health problems. Even if they are sending medication home or selling it, individuals will be aware that the level of study medication will be monitored. In order for the study medication to show on a blood test, it will need to be taken for a day or so before the study visit. THT (2010) reported an increase in calls from individuals asking if there is any danger with this practice. Others may be less concerned about the ramifications of over-participation. The benefits of the over-participation - such as continued access to treatment and supporting relatives - may be more attractive than the short term risk of additional blood tests and x-rays.

The development of physical problems relating to multiple-participation not only affects the individual but can have a detrimental effect on the scientific validity of the trial, which could impact on the treatment of future patients. Participation in a single trial carries some risks, but the preliminary animal research will have given researchers some idea of potential side-effects which might develop. Multiple-participation carries the additional risk of interactions between ARVs, which can occur if the individual is swapping drugs prior to each study visit. As the researcher will have

no way of knowing if the volunteer is taking additional drugs, any adverse reactions will be attributed to the trial medication. Adverse reactions in clinical trials are reported to the trial data managing committee. The role of the data managing committee is to look at all adverse incidents which occur to trial participants. Like the researcher, they are likely to attribute adverse reactions to the trial drug. If the reaction was severe they have the power to stop any clinical trial if they consider that the study medication is harming participants, or to ask that further recruitment is put on hold until a full investigation is completed. This will delay the trial and the potential development of a safer and more effective treatment for HIV.

Multiple-participation can affect the results of the trial in other ways. For example, Mulligan (2000) reported that one class of HIV medication, the protease inhibitors, are very effective at reducing the amount of circulating virus, but are known to cause an increase in lipids. If the trial is seeking to develop a new protease inhibitor with a better lipid profile and the participant continues to take another protease inhibitor as part of another trial, their lipid levels may remain high. Researchers may falsely assume that the trial medication had no effect on the lipid profile. While it is unlikely that the blood results of one volunteer could significantly skew the data, if several volunteers were also participating in other trials, researchers may conclude that the trial medication is not as effective as expected.

Drug swapping is another threat to the scientific validation of the trial. Participants in multiple-trials may be on different drug regimens. Anecdotal evidence suggests that

some HIV positive asylum seekers and refugees switch ARVs prior to a hospital visit to ensure that the trial drug will show in blood tests. This practice can lead to the development of drug resistance. During the development of new ARVs, researchers will establish if the study drug is safe, well tolerated and has a good resistance profile. If the researcher is unaware the participant has been exposed to other ARVs, resistance is likely to be attributed to the failure in the study medication. As with the safety profile of trial medication, it is unlikely that any one study would have large enough numbers of participants who are multiple-participating to seriously skew data. However, physicians review the results of clinical trials carefully when considering ARV regimes with a patient. They may choose not to use the new ARV if they have concerns around the resistance profile which could result in the patient missing out on a potentially good drug that would improve their quality of life. Anecdotal evidence from researchers working with HIV positive asylum seekers and refugees from African Community Organisations in the UK suggests that a significant proportion of individuals participate in concurrent clinical trials. However, as these figures are not collated, there is no way to substantiate these claims at this point in time.

Similar concerns are faced by individuals who 'over participate' in clinical trials. Participants in clinical trials are exposed to trial medications with unknown safety profiles and side-effects. They are required to have multiple clinical tests to establish the effects of the medication. In order to minimise these risks, individuals are required to wait at least twelve weeks between different trials. This enables any residual study medication to be excreted from the system and allows the volunteer time to recover

from any investigations. Individuals are clearly informed that they must not participate in more than one clinical trial at any one time. Despite the risks, some individuals do enrol in concurrent trials or do not wait the requisite amount of time between trials to allow the study medication to leave the body. Over-participation can also affect the scientific validity of the trial as there could be interactions between the residual drug from the previous study and the new trial drug. As before, side effects could be attributed to the trial medication, not to any drug interactions.

Solutions to over-participation and multiple-participation

One solution to this problem would be to exclude groups who are likely to engage in this behaviour from participating in clinical trials, thereby preventing them from being exposed to harm. This is problematic for a number of reasons. Firstly, over and multiple participation can be found in all types of clinical trials, not only HIV. While it may be possible to identify groups where there is a higher incidence of this practice occurring, it would not stop the practice. Secondly, only a small proportion of these groups would over or multiple participate. It would seem unjust to prevent the majority of individuals who want to participate from doing so to prevent harm to the few who do. Finally, prohibiting specific groups from participating in research would - in some situations - make it difficult to conduct research. For example, the number of HIV positive women giving birth each year is very small in comparison with the rest of the population. Clinical trials seeking to reduce mother to child transmission of HIV by nature need to be conducted within this population. If it were found that HIV positive pregnant women were more likely to over participate and were excluded from

participating in clinical trials, it would be very difficult to conduct research on this topic.

Boyce (2003) found that of seven thousand potential volunteers who were screened prior to participation in Phase One clinical trials between 1997-2001, sixty-eight (one in a hundred) had completed another trial within twelve weeks, even though they had signed a statement to the contrary. This concern was addressed by changes to clinical trials regulations. In May 2004, the European Union Clinical Trials Directive 2001/20/EC was put into practice in the UK through the Medicines for Human Use (Clinical Trials) Regulations 2004. Part 1, 1K of the regulation says that applicants to ethics committees should include information about procedures for checking potential subjects' possible involvement with other trials. The Medicines and Healthcare Products Regulatory Agency (MHRA) accreditation scheme for Phase One units requires units to have procedures in place to prevent over volunteering. Phase One units are also required to include a statement on the dangers of over participating on the patient information sheet and consent form. The Over Volunteering Protection Scheme (TOPS) was set up in Phase One clinical trials units to try and prevent volunteers from taking part in a clinical trial too soon after a previous one, or from taking part in two trials at the same time. Units were concerned that volunteers were risking their health by receiving too many potential new medicines from which they may get no benefit and having excessive clinical tests, in addition to compromising the quality of trial results. The scheme is free to all units which conduct Phase One trials, and uses National Insurance numbers to check when a volunteer completed their last clinical trial (Association of Human Pharmacology in the Pharmaceutical

Industry, 2011). Volunteers do need to be informed about the scheme and to give permission to have their details checked. This is done as part of the consent process, where volunteers are advised about the risks of multiple and over-participation in clinical trials. Should they decline to have their details checked, they will not be permitted to enrol. While some prospective volunteers have been unhappy with the scheme, most view it as standard practice and in their best interest (Boyce, 2011). The scheme has also been welcomed by the research community, as it has enabled them to fulfil their obligation to check that volunteers are not over participating. This helps to protect both the safety of the volunteer and the integrity of data. By 2007, TOPS reported that twenty-six Phase One units were using their data base. These units were situated in Scotland, England, Wales and Ireland. Eighteen of these units were run by research organizations, five by pharmaceutical companies and three were linked to universities. 53, 650 volunteers have been registered. Boyce (2003) found that in his Phase One unit alone - when checks were conducted prior to screening new participants – eighty-five volunteers had applied to participate in a clinical trial within twelve weeks of the previous one; one volunteer was already taking part in two trials at the same time. By 2004, the number of volunteers participating in two or more trials or entering too soon after a trial had dropped to eighteen in that unit. Boyce attributed this drop to volunteer's awareness of the scheme.

Despite the benefits of the TOPS scheme, it is only used in Phase One trials. Phase Two to Four clinical trials, where most of the HIV trials take place, do not have a mechanism where researchers can check if volunteers are multiple or over

participating. While researchers ask potential participants if they have recently, or are at present, taking part in another trial, they are dependent on the honesty and integrity of the trial participant to answer truthfully as they have no means of confirming their participation. If healthy volunteers present recent needle marks at a Phase One unit, researchers may be alerted to the fact that they have recently taken part in a clinical trial. However, as many HIV positive patients have blood taken regularly as part of standard care, additional needle marks would not raise any index of suspicion. In addition, the volume of HIV clinical trials being held in the UK would make it time-consuming for researchers to call round all units to establish if potential participants were already enrolled in a trial.

It should be possible to expand the TOPS scheme for Phase Two to Four trials. The ground-work has already been undertaken by Boyce and would only require the backing and co-operation of both the pharmaceutical industry and the regulatory authorities. The scheme would need to be adapted to take into account the specific challenges of asylum seekers and refugees. At present the TOPS scheme requires volunteers to provide a National Insurance number which is used to check if they have recently participated or are already participating in a clinical trial. However, many HIV positive asylum seekers and refugees will not have a National Insurance number. In addition, first names and surnames are often transposed or misspelled, while different family names are given which adds to the difficulty of identification. In order to overcome these challenges, a 'participant passport' could be developed for those wishing to participate Phase Two to Four clinical trials. This document would be

issued by the site where they first enrolled in a trial. For those who do not have a National Insurance number, passport details would also be required as well as Immigration documents. All participants would require a photograph, which had been countersigned by their physician. The individual's details would be registered on a main data base, which would be secure and only accessible by participating units, similar to that of the TOPS scheme. As with the current TOPS scheme, individuals would only be permitted to enrol in a clinical trial once these checks had been carried out. While some might argue that this scheme would be too difficult and too expensive to maintain, the current TOPS Phase One scheme works remarkably well and is supported by both researchers and the pharmaceutical industry. Others may be concerned that the scheme would be too time-consuming, increasing the time taken to recruit to trials. However, the present scheme has not found this to be the case. Individuals may also be concerned about the confidentiality of the scheme and the inadvertent disclosure of their HIV status. These concerns would be addressed by ensuring that the data base could only be accessed by named individuals who had been vetted by the scheme administrator. All procedures should follow the precepts of the Data Protection Act, and all participants in Phase Two to Four Trials would be required to register for the scheme, reducing any concerns about stigmatising any particular group.

Until such a scheme is in place, researchers need to be alert to the possibility of multiple and over-participation. When discussing clinical trials, they need to clearly explain the affect this practice can have both to the individual and the results of the

trial. Community groups can also be utilised to ensure that individuals are made aware of the harm this can do to their health, as well as potential harm to the development of new ARVs.

The obligations of the participants, researchers and ethics committees in relation to harm in clinical trials

Similar to protecting themselves from sexual harm, participants also have some obligation to protect themselves from trial related harm. To make an autonomous choice regarding participation, individuals need to have enough information to base their decision on. All clinical trial participants are given a participant information sheet (PIS) which should inform them of any advantages and disadvantages of participating as well as any risks and benefits. In the case of over and multiple participation, the PIS only asks participants if they are, or have recently, participated in a clinical trial. It does not give a reason as to why they are being asked these questions. Once informed of the risks, potential participants can make an informed choice to avoid these practices.

Individuals also have an obligation to ensure that they are clear about what is being asked of them should they agree to participate. Outside a clinical trial, we would ask for an explanation if, for example, our employer asked us to do something which was out of the ordinary. In doing so we would be protecting our own interests. It would be foolish to agree to something written in the PIS that we either don't understand or don't want to do. For example, the number of additional study visits may be a

deterrent to some people. Others may be willing to undergo the additional visits, if given a clear explanation as to why they are necessary by the researcher. Potential participants may also need a clearer explanation of clinical procedures than the one provided in the PIS. I have seen a PIS where a lumbar puncture was described as a painless procedure involving a 'sharp scratch' to the back. Having asked and been given a more detailed explanation by the researcher, the potential participant firmly declined to offer to participate.

While the clinical trial will have had ethical approval, there may still be some level of harm associated with the trial. Participants may choose to disregard this harm due to personal beliefs or circumstances. For example, they may have had a close relative die of a particular condition, and wish to further their knowledge of that condition. Some might feel that researchers are only required to make sure the participant knows the risks, but they should not be responsible for eliciting why the individual has chosen to participate. They might argue that providing information about the trial and outlining any potential risks and benefits enables participants to make an autonomous choice. A stronger view is that they should exclude those who are at increased risk from taking part in the trial, if, based on their knowledge of the client group, they anticipate the actions of that individual. An example here would be if the researcher had knowledge that the prospective HIV positive participant was from a refugee background and would have a greater risk of developing resistance. The researcher might refuse that individual access to the trial to protect them from developing resistance. The harm, development of drug resistance, is not caused by the

researcher, but may be additional risks of participation. Researchers have a general duty of care to safeguard participants from harm, based on the principal of non-maleficence. While it may not always be possible to prevent harm - such as expected side effects of trial drugs - they can take measures to minimise these risks. This needs to be balanced with respecting the autonomy of the individual to make an informed choice based on the information given. If the benefits of participation outweigh the harm, the individual should be permitted to enrol in the trial.

Role of the Ethics committee in preventing harm

COREC (2009) states that the role of the ethics committees is to 'protect the rights and well-being of research subjects'. One way in which they do this is by reviewing and giving an ethical opinion on research protocols which are submitted to them. When reviewing a protocol, they take into consideration the potential risks and burdens to participants. These can include number of study visits, the number and nature of any tests and the potential of the study to cause injury, distress and discomfort. Researchers are also required to produce a participant information leaflet (PIS), which outlines these risks and benefits. The PIS and the role of the ethics committee will be discussed in more detail in chapter 6. The REC bases its decision on the information given by the researcher in the protocol and the knowledge of the individual REC members who review the protocol. If the REC members have limited knowledge of the condition being investigated, they may seek the opinion of an expert. If the REC is of the opinion that the proposed research could be harmful to participants, they will require the researchers to justify why they are potentially

exposing participants to harm. If the researcher can demonstrate that they have tried to minimise the potential risks, and that the research could not be undertaken in any other way, the REC may decide that the research should go ahead, providing that the risks are fully outlined in the PIS. RECs are under some pressure from NRES not to reject proposals, as this could slow down research and in the case of clinical trial, see research being taken abroad. As such, some trials which the REC may consider ill-conceived but of little risk to the individual participant may be accepted. Once trials have been approved, RECs require researchers to submit regular reports - including safety data - on a regular basis. Clinical trials themselves are also monitored to ensure that the protocol is being followed; this is assessed by auditing trial related documents. While the paperwork for a trial may be completed correctly, auditors have no means of assessing how researchers approach individuals about the trial, provide them with information or recruit them.

Potential benefits for HIV positive asylum seekers/refugees who participant in clinical trials

Information sheets relating to clinical trials inform prospective participants that they may not benefit from the study medication. Indeed, they may experience additional side effects of the study drug and be burdened by hospital visits and tests. However, participation in a clinical trial may benefit the participant in other ways.

Potential access to treatment and care

As I have discussed earlier, access to on-going NHS care for failed asylum seekers

and refugees is at best patchy, as NHS Trusts interpret the guidelines very differently. Individuals who have been prescribed HAART prior to their asylum claim being rejected should be able to continue. However, the Terrence Higgins Trust (2009) reported that this does not always happen. Some individuals have been told that they are no longer eligible for NHS care, and have been denied access to HAART. In order to continue treatment, individuals may consider accessing a clinical trial. While the trials are usually conducted in NHS premises, HAART and associated tests are funded by the pharmaceutical industry. Under the Declaration of Helsinki (2008), doctors conducting clinical trials are responsible for the physical well-being of individuals under their care. While this guidance relates to any potential side-effects as a result of the trial, it would be very unlikely that doctors would disregard any other health-care issues that an individual presented during the course of the study. Any new symptom or illness may be related to the trial drug and would need to be investigated, treated and recorded as an adverse reaction. As such, participants are advised to contact the team should they experience any unexpected physical symptoms during the duration of the trial. While asylum seekers and refugees may not be eligible for NHS treatment and care until the cause of the illness was established, any tests and treatment would be met by the study. Those individuals with a low CD4 count and high viral load may be on additional medication such as prophylaxis for other conditions, or taking the antibiotic cotrimoxazole to prevent PCP. It is likely that they would continue to have access to these medications as part of the clinical trial. Access to medications for other conditions would be at the discretion on the clinician conducting the trial. These should be discussed with the individual prior

to recruiting, as part of the consent process which will be discussed in chapter 7.

Psychological benefits

Participation in a clinical trial may also have psychological benefits for the individual. Feroze (2012) suggests that individuals living with chronic medical conditions experience greater levels of anxiety and depression than any other groups of patients. Silove (1997) also found that asylum seekers and refugees had much greater levels of anxiety and depression than that of the general population. Having both may enhance the psychological distress. Whetten (2008) described the feelings of those newly diagnosed with HIV. For many, initial concerns about future health are reduced when they commence on HAART, replaced by optimism for the future. However, once the availability of HAART is removed, this optimism is removed, and replaced by fear of the future. Participation in a clinical trial where they can continue HAART may alleviate some of the psychological distress and buy them some time to explore other alternatives. In addition, those participating in clinical trials may take some comfort in knowing that should they develop a medical problem, they will have access to medical care. Hutchinson (1998) found that psychological benefits of participation included being able to express concerns about their medical condition and concerns about long term prognosis. The Medical Foundation for the Care of Victims of Torture (2008) found that many asylum seekers have undergone violence and trauma. HIV clinical trials in the UK are usually conducted within established NHS clinics - where staff are experienced in dealing with these issues. They generally have close links with external organisations including the Medical Foundation for Victims of

Torture. If a participant on a clinical trial is identified as having trouble dealing with past experiences, they can be referred to the appropriate organisations. In addition to providing psychological support, the organisations may also be able to provide practical support, such as food and access to safe accommodation. HIV positive asylum seekers may also experience social problems. In addition to lack of food and shelter, they may find it difficult coping with a new culture and possible language difficulties. Participants in clinical trials will be able to access support organisations which work closely with clinics - who can offer a whole range of services ranging from practical to social support.

Benefits to sexual partner

HIV is primarily transmitted during unprotected sexual intercourse. Many people diagnosed with HIV are in sexual relationships. When they are initially diagnosed, their clinician will have advised them to practice safe sex in order to protect current or new sexual partners from becoming infected by the virus. They will also be advised that practicing safe sex will protect themselves from contracting other strains of HIV, which will be detrimental to their health. Condoms are recognised as the best protection against sexual transmission of HIV. However, even if used consistently and correctly, condoms may break or fall off, and they are only ninety-eight percent effective in preventing pregnancy if the incident were to occur during the woman's fertile period. As such, those using condoms to avoid an unplanned pregnancy are advised to use an additional method of contraception. Studies suggest that a ninety-five to ninety-seven percent efficacy rate is much more realistic in general use

(Faculty of Sexual and Reproductive Health, 2007). One can assume that if there is a risk of pregnancy, there is also a risk of HIV transmission. A broken condom can allow both the passage of sperm and seminal fluid, the latter being the vehicle for HIV transmission. When a patient is first diagnosed with HIV, they will be encouraged to bring their partner along to be tested. Safer sex will be discussed in detail, and a supply of condoms given. If their partner is found to be HIV negative, the use of PEPSE will be discussed with the couple. If a discordant couple have a condom incident, accessing PEPSE is considered a medical emergency. While it is available in A&E departments, its use is normally limited to those who have been at risk of contracting HIV through a needle stick injury. Despite the BASHH (2008) recommendation that it should be available for high risk sexual exposure to HIV, some staff in accident and emergency departments are not well versed in its use. HIV positive patients who have arrived over the weekend have been told to return on Monday to see the doctor in charge. As PEPSE is only effective within seventy-two hours of unprotected sexual intercourse, the window of opportunity for taking the medication has gone.

While BHIVA/BASHH (2011) recommend that physicians discuss safe sex with patients at each clinic visit, this may be impossible due to time constraints. If the individual enrolls in a clinical trial, the researcher will again discuss safe sex. This is of particular concern in trials involving new ARVs where there may be potential risks to an unborn child. Participants will be encouraged to use another form of contraception - in addition to condoms - to protect against pregnancy. The researcher will also

discuss the potential risks of transmission to the partner and will encourage the patient to bring them along to discuss safe sex. The researcher will discuss the use of PEPSE and will ensure that a supply is made available to the participant and their partner.

The participant may not be in a sexual relationship when they first enrol in the trial, so while PEPSE will be discussed, its use may not be applicable at that point. However, as HIV clinical trials tend to be conducted over a long period of time, it is possible that participant will form a new relationship during the course of the trial. While discussing safe sex with participants may not be within the scope of the research, most researchers will be happy to discuss any concerns participants have and refer them to the clinic health adviser who will be able to address any issues in more depth.

Participation in a clinical trial will benefit both the individual and their partner. As a failed asylum seeker, they may not be able to access PEPSE following a condom incident. However, as a trial participant they will have been given a five day 'starter pack' which will enable them to initiate treatment within the recommended time. This will reduce the risk of the partner contracting HIV. The medication in the starter pack will have been carefully considered, taking into account the trial regime of the index patient and the BHIVA (2010) guidelines on PEPSE. This will ensure that the PEPSE regime is effective and will also reduce the risk of the partner developing resistance. Should the partner have any questions about the medication or experience any side effects, they will also be able to use the twenty-four hour telephone helpline available

to trial participants.

Health improvements

Braunholtz (2001) and Lantos (1999) suggest that individuals participating in clinical trials tend to do better than those who receive standard medical care. One proposed reason for this is the increased length of time spent with staff. Field (2010) reported that GP's were concerned that they could not fully assess a patient in the seven minutes they had allocated. In such a brief consultation, patients do not always have time to assimilate what they are being told, let alone formulate any questions. Patients may have health issues they wish to discuss which cannot be comprehensively covered in such a short visit. In contrast, when an individual is considering participating in a clinical trial, the researcher is required to spend time discussing the trial with them. Most clinical trials require that the patient is given at least twenty-four hours to consider participation prior to giving consent. During that time, they are asked to discuss the trial with other people and list any questions they would like to ask. When they meet with the researcher prior to signing the consent form, they are again asked if they have any questions. This may be the first time that patients have felt they have been given time and permission to ask questions about their illness. When the patients enrol in a trial, they usually find that the doctor or research nurse will spend much more time with them than they would do during a normal clinical consultation. This is primarily to ascertain if they have developed any clinical effects of the trial drug. It may also make the individual feel that they are valued and more inclined to attend their next study visit. Trial participants often

remark that they feel much more involved in their care, as they have more information and are actively encouraged to ask questions. For some this may be an empowering experience.

HIV positive asylum seekers and refugees may also benefit from the Out of Hours service provided in clinical trials. Participants are also encouraged to contact the researcher should they experience any new symptoms or become unwell during a trial. Following the phone call they may be asked to return to clinic for an unscheduled visit. If this happens out of hours, the researcher will arrange to meet them in the hospital. Trial participants comment that this is very different from the out-of-hours service they have in standard practice. Patients who become unwell when the clinic is closed are advised to contact their general practitioner. This can be problematic if the GP is unaware of their HIV status. Some GPs may not be fully conversant with HIV infection and may suggest that unless the problem is urgent, they should wait and see their regular HIV consultant. This may be detrimental to their health as some HIV infections need urgent attention to prevent complications. Some HIV positive asylum seekers and refugees may not have a GP, as they may not be eligible for NHS treatment and care. As such, participating in a clinical trial will enable them to have access to medical treatment over the weekend which they would not have had otherwise. In an emergency, patients are advised to attend their local accident and emergency department. In contrast, Gunn (1998) and Peppercorn (2004) found no difference in outcomes of those who participated in clinical trials to those who did not. It is difficult to apply the findings of their study to HIV positive asylum seekers and

refugees as their cohorts were all eligible for health care. For HIV positive asylum seekers and refugees, the main benefit of participation would be continued access to treatment.

West (2005) suggested that any improvements the participants experience during a trial may be due to staff following protocols rather than providing additional care. Again, HIV positive asylum seekers and refugees were not represented in the cohort.

Summary

Participation in clinical trials for all HIV positive individuals carries both risks and benefits. While the risks of participating in a clinical trial may be greater for asylum seekers and refugees - due to potential of developing drug resistance - the benefits of participation outweigh any harm.

Unless antiretroviral therapy is stopped in a structured manner, resistant strains of HIV will develop. HIV positive asylum seekers and refugees are at a greater risk of developing drug resistance as they may be detained or deported with little notice, resulting in abrupt withdrawal from treatment. Should they develop a resistant strain of the virus, treatment options are reduced. Even if treatment is available, which it may not be if they are deported, it is likely to be much more expensive than standard therapy and may not be as effective.

While these are strong arguments against participation, the potential benefits of

participation for HIV positive asylum seekers and refugees outweigh any harm. While they may be an increased risk of developing drug resistance, asylum seekers and refugees are at more immediate risk if they are unable to access HAART. Without participating in clinical trials these individuals would be unable to have continued access to antiretroviral therapy, and within a few weeks without therapy they will see an increase in their viral load and a decrease in CD4 counts, leading to the development of opportunistic infections and eventually death.

Not all HIV positive asylum seekers and refugees will benefit from participation in a clinical trial. They may not respond to study medication, or develop side effects which necessitate stopping HAART. Others may not be eligible to participate for clinical reasons. For those that do enrol in clinical trials - provided that they are aware of the risks of developing drug resistance and can take measures to reduce these risks - the immediate risk of death is greater than the long term effects of drug resistance.

Chapter 6

Consent – provision of information.

Introduction

The Declaration of Helsinki (2008) Article 24, states that participants in clinical trials should be provided with both written and verbal information about the proposed trial. While this may appear to be a simple requirement which is easily fulfilled, researchers often struggle to provide information sheets (PIS) which are easily understood by prospective participants. Several studies have shown that participants do not understand what they have read in the PIS. Akkad (2006) asked individuals who had participated in various types of clinical trials to complete a questionnaire which would assess their understanding of the information they had been given. Joffe (2001) conducted a similar study asking individuals who had participated in cancer trials to complete a questionnaire to assess their understanding of the trial. Both found that participants had understood the trial to some extent, but were unclear as to the difference between standard treatment and drug giving in a clinical trial setting. Some believed that they would benefit from participating, despite being told otherwise by the researcher. All were satisfied that they were not coerced to participate, and felt that they had been treated well by research staff. While I am glad that the participants reported that they were well treated, I am a little concerned about their lack of understanding of the information they had been given. While the participants were given information, it does not appear from these studies that researchers made any effort to check that the participants had understood what they were consenting to.

In this chapter I will look at how the provision of information to prospective participants can be improved, including the challenge of providing information to HIV positive asylum seekers and refugees. This chapter will first focus on the limitations of the current system. I will argue that changes need to be made in order to enhance understanding for all participants. In the second half of the chapter I will discuss ways to improve the provision of information to prospective participants. I will argue that Research Ethics Committees (RECs) need to be more proactive when reviewing applications, to ensure that the PIS reflect the information needs of the target population.

Importance of consent

Seeking informed consent respects the individual's autonomy. Harris (2004) suggested that the need for consent arose from the desire to respect the autonomy of autonomous beings. In clinical research, individuals who are thinking about participating should be given enough information on which to base that decision. Ensuring that they have enough information to make an informed choice helps to support their autonomy. Mclean (1997) suggests that good research should not only be scientifically sound but must also at all times respect the participant. Failing to provide adequate information demonstrates lack of respect for the prospective participant. This view is supported by Kale (1997) who states that research without the patient's consent is unethical in any part of the world because it violates the fundamental right to autonomy and self-determination. While I have no disagreement with this assumption, I would also add that consent based on ambiguous or unclear

information is also unethical. Consent cannot be said to be informed if the participants understanding of the trial bears no resemblance to the aims and objectives stated in the PIS. For example, many HIV positive asylum seekers and refugees do not have English as a first language. While they may be able to understand spoken English, and have some degree of literacy, some may have difficulty reading and understanding participant information sheets. For this population, the provision of an information sheet alone may not be sufficient to guarantee understanding. If participants cannot understand the information they have been given, they cannot give informed consent. As such, research conducted under these conditions may be unethical. Let us look at this in more detail. As well as respecting the participants' autonomy, the provision of information in the consent process also helps both the researcher and the individual to avoid unrealistic expectations. As discussed previously, some HIV positive asylum seekers and refugees erroneously believe that enrolling in an HIV clinical trial will support their asylum claim. Those who enrol in a trial for this purpose only to find that their participation was not taken into consideration, and that their appeal has been unsuccessful, will be very angry and may believe that they have been misled by the researcher. Has the researcher behaved in an unethical manner? They have followed the NRES guidance by providing the prospective participant with a PIS, waited twenty-four hours before providing them with an opportunity to discuss any issues, and only after that sought consent. They didn't set out to deceive the individual by failing to mention immigration issues. Indeed, they could argue that immigration did not cross their mind when discussing the study. As such, it would appear that they have not intentionally meant

to cause harm or distress to the participant. However, the omission of information reflecting their immigration status in the PIS may have caused that individual to enrol in a trial under a false assumption. It could be argued that the prospective participant should have asked this question of the researcher as they had sufficient time to consider any questions prior to enrolling in the trial. While it is unrealistic for the researcher to be aware of every issue that could influence each individual's decision to participate in a clinical trial, it is not unreasonable to expect researchers to be aware that those approached to participate in HIV clinical trials may be asylum seekers or refugees. As such, the information in the PIS should reflect the issues which are specific to this population. This will enable prospective participants to consider all pertinent information prior to agreeing to participation. This lack of understanding was reflected by McCluskey (2005). She found that individuals recruited to HIV vaccine trials displayed flawed beliefs about the trial. She reported that prospective participants were 'misinformed, made erroneous assumptions and had unrealistic expectations of the trial'. Some of these individuals thought that they could become infected as a result of the study, while others thought that participating in the trial would afford them lifelong protection from future exposure to HIV. In both cases, the participants had been given a participant information sheet. It is unclear why they did not understand the information. The language used in the participant information sheet may have been too technical for the individual to understand, or they did not take time to read it or discuss it in more detail with the researcher. It is clear that HIV positive asylum seekers and refugees have specific needs in relation to the provision of information about clinical trials. If researchers are aware of these

needs and do nothing to address them, they are failing to demonstrate respect for the individual's autonomy.

Provision of information-current practice

Various research bodies have provided guidance on the elements which should be included in a patient information sheet, in order for individuals to make an informed choice when deciding to participate in a clinical trial. The WHO (1993), g.3.states that in order for informed consent to be valid, a researcher has to:

- Communicate to the prospective subject all the information necessary for adequately informed consent
- Give the prospective subject full opportunity and encouragement to ask questions
- Exclude the possibility of unjustified deception, undue influence and intimidation
- Seek consent only after the prospective subject has adequate knowledge of the relevant facts and of the consequences of participation, and has had sufficient opportunity to consider whether to participate.
- Obtain from each prospective subject a signed form as evidence of informed consent

This view is supported by the Medicines for Human Use (Clinical Trials Regulations) 2004 which states that; 'A person gives informed consent to take part in a clinical trial

only if his decision.... is given freely after that person is informed of the nature, significance, implications and risks of the trial'... Mason and McCall (1991,p98) go on to add 'the patient's consent must be based on four lines of explanation: the purpose of the experiment, the benefits to the patient and society, the risks involved and the alternatives open to the subject'.

The Declaration of Helsinki (Article 24) requires researchers to inform potential trial participants of the aims, methods, anticipated benefits, potential harm and hazards of participation as well as their right to withdraw from the trial after giving consent.

The International Conference on Harmonization ICH (1996) lists eight basic elements which should be included in the participant information sheet:

1. A statement that research is being conducted, its purpose, duration, and description of experimental procedures to be employed
2. Description of foreseeable risks and discomforts to the subject
3. Potential benefits to subjects and others
4. Description of alternative treatments
5. Statement regarding confidentiality of records
6. Arrangement for compensation should the subject be harmed
7. Contacts for further information or redress
8. Statement that participation is voluntary and participants can leave without any negative consequences on further treatment

These elements are incorporated in both the Royal College of Physicians (1990)

s.7.14, and the Association of the British Pharmaceutical Industry (1992) guidelines for producing participant information sheets.

While these guidelines differ on minor points, they all allow prospective participants to be informed of the nature of the trial, including any risks and benefits. They also all state that the trial is voluntary. However, none of the guidelines suggest how the researcher can be assured that the prospective participant has understood the information they have been given. It would appear that providing information alone is enough to fulfil the guidelines. As I illustrated earlier, researchers and participants may have a very different understanding of the information provided. As such, participants could agree to participate without fully understanding the implications.

In the previous chapter I briefly discussed the role of the ethics committee in preventing harm to clinical trial participants. In this chapter I will look more closely at the role of the ethics committee in the provision of information to prospective participants. As part of the process to gain ethical approval for a clinical trial, researchers are required to submit participant information sheets (PIS) with the other trial documents to the ethics committee. NRES (2011) provides a range of PIS templates for various types of trials in addition to comprehensive guidance for the researcher. Researchers are permitted to develop their own PIS; however this should contain the eight basic elements described above. NRES (2009, 5.1.2) suggests that the length of PIS should reflect the type of study. For example, studies with little intervention and minimal risk such as those involving administering questionnaires

are likely to need a shorter PIS than a more complex high trial which involves clinical investigations and the administration of study medication.

In recent years pharmaceutical companies have justifiably become more concerned with possible litigation from trial participants. KPMG (2011) reported that pharmaceutical companies had paid US\$19.8 billion to settle US law suits. As such, the PIS produced by these companies have increased in length to incorporate every potential side effect to reduce the company's liability. It is not unusual for prospective participants to be given a PIS that is more than twelve pages long, which includes information both about early animal studies, as well as all manner of side-effects displayed in first-in-man studies, (which may or may not have been as a result of the medication). Some sections are written by company lawyers and are meaningless to the lay reader. While the company is to be applauded for providing detailed information for the prospective participant, it is likely that an excessively long and detailed information sheet may hinder rather than enhance understanding. Some trials provide a short one page summary of the trial - to enable prospective participants to see if they would be interested in the trial. They are then advised to go on to read the full version if they are considering participating. Again concerns have been raised that decisions are being made on the short form, as the full version is too daunting to read. Information which could be pertinent to that individual, such as time spent in the trial, could be missed. Some researcher's ethical interests may also advocate for a longer PIS, to ensure that prospective participants are given enough information about the trial, thus enabling them to give informed consent.

Despite the NRES (2007) guidance on producing written information, the REC I sit on regularly reviews submissions which include incomprehensible PIS. They are often too long, too technical, unclear, and don't fully reflect the aims and objectives outlined in the protocol. Researchers are required to modify these prior to gaining ethical approval. The amended forms are reviewed by the sub-committee, which may or may not include a lay member. These are generally improved, but while they may be easier to understand for the REC member, they may still be difficult to understand by a lay individual. While lay members of the REC may not be medical, they are generally educated to a high standard. What is comprehensible to them may not be understood by participants. Ethics committees recognize the short comings of the PIS. Ames (2008) was keen to elicit the view of members of research ethics committees on the standard of patient information sheets for randomized controlled trials. The committees were asked to offer suggestions on ways to which information could be improved. Members of the ethics committees were concerned that the patient information sheet did not fully explain randomization. They felt that it was unlikely that trial participants could make an informed choice on the information given. Those interviewed suggested that trial participants should be provided with more information about the methodology of randomized controlled trials in language understandable to wider public. They go on to suggest that this should be followed-up with a face to face explanation by a researcher who is well versed in randomization and able to answer any questions. If RECs are aware that of the short comings of PIS, why do they still approve them? This may be in part due to pressure not to slow

down research. Pharmaceutical companies contribute a substantial amount to the economy of the UK. In its 2010 report, the ABPI found that the pharmaceutical industry brings greater economic benefit to the UK than any other high-tech industry, figures which were supported by The Office of Health Economics (2010). Slowing down research by increasing the time to approve trials could drive researchers away from the UK to other countries, where it may be easier to gain approval. Subtle pressure may be placed on RECs not to slow down research by rejecting studies.

Some of the challenges of incomprehensible information could be addressed by utilising patient group representatives in the development of the PIS. NRES (2011) already recommends involving patient group representatives in study, but this suggestion is not always acted on. One of the advantages of such groups is the insight they are able to provide on the target population. In HIV trials, voluntary organisations such as Body and Soul and Positively Women have developed a strong relationship with researchers and have been consulted on user involvement in research, as well as the design of participant information sheets. While the RCP (2007) found that asylum seekers and refugees were difficult to engage in research, this has not been the case with HIV voluntary organisations. Many provide support for this group and are in regular contact with members. Groups may be willing to facilitate engagement with researchers whom they have developed a trusting relationship. By working with user groups, researchers can develop PIS's which are easily understood and culturally appropriate. They can also use this as an opportunity of 'sounding out' the target population to see if the proposed research would be

feasible within the population. One of the disadvantages of utilising patient groups is that they may not be representative of all the target populations. For example, a group of Somali men could not provide insight into the needs of Ugandan women. There may also be peer pressure on individuals to get involved with research.

Once the PIS has been developed, it should be piloted with patient group representatives. This process will highlight any recurring problems which arise such as the phrasing of specific sections. The researcher could also ask the group's views on how to engage with prospective participants. For example, I was involved in a study where the target population was HIV positive teenagers. As part of the study, the young people were expected to complete a two hour visit where they were asked to complete questionnaires and undergo neurocognitive tests. Prior to the neurocognitive element of the visit, they were offered refreshments to aid their concentration. For the pilot study we provided healthy fruit and sandwiches. The focus group were less concerned about the two hour visit than our 'appalling' choice of food! They suggested we switch to doughnuts and crisps, which would be much more attractive to teenagers. Acting on their suggestion, we changed to the less healthy option for the main study, which was much appreciated by participants. The group also suggested conducting interviews after school and at weekends, which again has proved to be popular with the participants in the main study.

In addition to the content of the PIS, RECs also review the language. Aspinall (2005) suggests that the number of people who have difficulty understanding written English

in the UK ranges from between 400,000 to 1.7 million. This includes those who have English as a first language. The Royal College of Physicians (2007, 5.51) estimates that 'spoken English is more often absent than present' in adult refugees. In order to aid understanding, NRES (2011, 5.1.4) suggests that the PIS is written in simple, non-technical terms which will be understood by lay people. It goes on to give very clear guidance on how to assess the readability of the PIS and suggests that it should be sent to organisations such as the Plain English Society who will offer guidance if needed. Understanding technical terms used in participant information sheets can be a challenge for all prospective research participants. This is especially problematic when the trial participant does not have English as a first language, such as the majority of HIV positive asylum seekers and refugees. All too often RECs review clinical trials where the researcher has identified that the target population does not have English as a first language. Despite this, they do not plan to translate the PIS, stating that they will only recruit individuals who can understand English. While this does not take into account those individuals who can understand English but may have difficulty with the written language, it also excludes a large number of the target population who may contribute valuable clinical information to the study. The Royal College of Physicians (2007) states that asylum seekers and refugees may have specific health needs. However, if they are excluded from research due to lack of English, it is unlikely that these needs will ever be identified or acted on. Those researchers who do identify that their intended target population does not have English as a first language may arrange for the PIS to be translated. However, this too may be problematic. In some African countries - such as Uganda - there may be

several languages in general use. It would be impractical to produce such a wide range of PIS. As such, some individuals may be unable to access the PIS in a language they can understand and would have no information to base their decision to participate, thus being unable to give informed consent.

Once the REC has approved a trial the researcher can begin to recruit. NRES (2011) suggests that prospective participants have at least twenty-four hours to read and consider the PIS prior to giving consent. There may be exceptions to this; for example, in trials involving emergency situations it would be impossible to delay treatment. At first glance, providing prospective trial participants with information looks easy. They are presented with the information sheet by a member of the research team and asked to read and discuss it with relatives and friends. Following this, they arrange an appointment to meet with a member of the research team who asks if they have any questions based on what they have read. Once these have been satisfactorily answered, the individual is asked to sign the consent form. Unfortunately, this process is seldom as streamlined in practice as it is in theory. Participants may lose the information sheet and miss follow-up appointments with research staff. By the time they attend the rescheduled appointment with research staff, they may have forgotten the initial discussion, thus restarting the process.

Information about the trial can be communicated by any member of the research team. How this information is given may influence the individual's decision to participate. The initial discussion of the trial may be left to the less experience

members of the research team such as junior doctors. In the UK, the General Medical Council (2009) requires that undergraduate doctors have communication training. Each medical school sets its own criteria and the amount of training varies between institutions. As in all disciplines, communications skills are perfected over time. There will be some junior doctors who are confident and competent communicating with patients, while others might find it more challenging. Their communication training may have equipped them to communicate bad news and to take a sensitive history, but they may not yet have developed the skills to ask patients to participate in a research study which may or may not benefit them. Experienced researchers are able to deal with questions such as 'what would you do if you were in my position'? Those with less confidence are often reluctant to provide a response to this question. While this may be due to their concerns of unduly influencing the individual, it often makes for a very stilted conversation with the likelihood that the potential participant feels that their questions have not been fully answered. Sokol (2007) suggests that this can be addressed by phrasing the response to enhance the individual's understanding of the study. He suggests that that answering questions forms part of informed consent process and enhances good patient centred care. In addition to enhancing the understanding of clinical trials, these communication skills can be adapted to enhance communication in other clinical settings. In contrast, Brown (2000) found that junior members of the research team may feel under pressure to recruit participants. Whether this is a real or perceived concern, it may affect the way in which information about the trial is conveyed to patients. They may present information about the trial in a more positive light, playing down any potential risks or burdens to the prospective

participant. I feel that communication with patients is a very important skill. As well as imparting knowledge about care, it enables patients to discuss concerns they may have about their own health and that of loved ones. As part of their training, junior doctors will be expected to give patients the results of tests including cancer. The skills they have learned to give such a difficult diagnosis can be transferred to discuss clinical trial, which is by far much less daunting. What may be more problematic is knowing how much information to give a prospective participant. As we have seen, the information contained in PIS varies. The researcher should be familiar with the trial protocol, which contains a more detailed account of the trial than can be found in the PIS. Less experienced researchers may stray away from the standard text in the PIS, and give background information which is not pertinent to their participation. Some participants may also want more information than is provided, while other may be disinclined to read even the basic information.

The Royal College of Physicians (2007) states 'the impracticality of giving full information has led to the saying there is no such thing as informed consent'. Gillon (2001) also supports this stance stating that fully informed consent is not attainable as it is always possible to add more information than that already given. In order to address this issue, Gillon suggests that the term 'informed consent' should be replaced by 'adequate consent' for less onerous trials, or 'extensive consent' for those trials carrying a greater possibility of risk to the individual. He suggests that the level of information provided to the individual should reflect the risk involved in the study. The two tiered system would require researchers conducting 'simple' trials, such as

those involving minimal risk to the participants, to provide a very short patient information sheet for participants followed by a short discussion. These individuals would then be required to give 'adequate consent' prior to participation. More risky trials would require the participant to give 'extensive consent'. This would involve providing the participant with a longer and more complex information sheet and require the researcher to spend additional time with the individual to ensure that they have understood what is required of them. While this is similar to the current NRES guidance where the length of the PIS should reflect the type of study, the current guidelines require all information sheets to contain the basic eight elements of consent. Gillon's model also challenges the current thinking that there should only be one level of consent. Is it possible to have different levels of consent based on the provision of information? I find Gillon's model problematic for two reasons. The first of these concerns the level of information provided for those in the 'adequate' consent group. The eight elements already required by NRES contain basic information which is applicable to all types of studies. It is very unlikely that prospective participants would not wish to be informed about the purpose of the trial or to know if there are any risks and/or benefits of participation. They will want to know that they are under no obligation to participate, and if they do choose to participate any information they give will be treated with confidence. They will also want to know that there are arrangements in place should they be harmed and to have a contact number for the researcher. Without such a basic level of information, it is difficult to see how prospective participants can give even 'adequate' consent.

The second problem I have with Gillon's model is who would decide if the information provided would lead to 'adequate' or 'extensive' consent. For some trials, the decision would be easy. Research which involved only the administration of a questionnaire would generally need a less extensive PIS than that of a clinical trial or a new medication. However, leaving the decision of which level of consent a trial would require to the researcher could lead to disparity. To illustrate, let us look at a fictional trial medication for acne. Researcher one may be paternalistic and wish to spare the participant worry. As such, he may choose to provide them with the adequate information sheet which does not outline the potential side-effects of the study. His rationale may be based on the small possibility of actual side effects against the worry the participant may experience thinking about these side effects. Unlike researcher one, researcher two may have a strong bias as to the potential good of the trial medication. To encourage participation he may provide participants with 'adequate' information, which again does not mention side effects. In contrast, researcher three believes strongly in maintaining the patient's autonomy. He might feel that the patient should be given as much information as possible to make an informed choice about the new medication. This researcher firmly believes that participants in all studies - even those felt to carry minimal risk - should be given extensive information. From this we can see that even if Gillon's model were to be adopted, guidelines would need to be established outlining what trials would require adequate and extensive information.

While Gillon's model offers different levels of information leading to adequate and

extensive consent, Eriksson (2004) suggests that potential participants should be able to choose the level of information they want about the trial, as potential participants are often discouraged by the length of the PIS and would rather base their decision to participate on the discussion they have with the researcher. Like Gillon, he suggests that there should be two information sheets for potential participants - one with limited information of the trial and a more extensive sheet for those individuals who want more information. However, unlike Gillon, he suggests that participants are allowed to choose which level of information they want. This is supported by Smith (2010) who found that some individuals 'devour' information about trials, while others 'can't be bothered putting on their glasses'. At present, NRES (2011, 5.1.3) suggests that a summary sheet can be provided in more complex trials. This should include the voluntary nature of participation, what the study involves, risks and benefits and alternatives to participation. If participants go on to express an interest in the trial they are provided with a longer PIS which contains additional information. While Eriksson's model offers the participants more choice than Gillon's, it does not fully ensure that participants have a basic level of information to base their consent. Participants who have read only the short version could be missing vital information which would influence their decision to participate.

Eriksson and Gillon have both offered solutions to the challenge of ensuring that individuals are provided with enough information to give informed consent. Gillon suggests that there should be two levels of information, followed by participants giving either adequate or extensive consent. Eriksson suggests that the researcher should

offer the patient the choice of a long or short version of the PIS, leaving them to decide what level of information they need. I do not think that Gillon's two tiered system of consent would be practical or indeed effective, nor do I think that participants should be given a choice of information sheets. However, I do concede that the current method of providing information to prospective participants is not effective. While I would argue that it is not necessary - or indeed practical - for participants to be informed about every aspect of the trial; I would argue the importance of keeping the eight elements. The current NRES guidelines suggest that researchers produce a summary sheet in addition to the main PIS for more complex trials. There is the risk that participants only read this and disregard the rest of the information. It is also impossible to compel prospective participants to read information sheet, no matter how long or short they are. Nor do we really know many participants actually read the PIS.

Some individuals actively choose not to read the PIS, preferring to be guided by the information they receive from research staff. Despite some researchers feeling that the research participant does not require in-depth information about any proposed trial, most researchers/doctors would be very reluctant to consent a prospective research participant who refuses to receive any information. Researchers have a legal obligation under the Declaration of Helsinki (2008) to provide information which will enable the individual to make an autonomous choice on whether to participate in a clinical trial. Steiner (2006) strongly feels that research participants should not be permitted to reject information. He is concerned that by choosing not to have

information about the trial, the individual puts himself at risk of being taken advantage of by an 'over enthusiastic' researcher. Kihlbom (2007) disagrees with Steiner, arguing that patients are exercising their right to autonomy by giving negatively informed consent. It would appear that it is the duty of medical staff to protect participant's autonomy by providing information, while potential participants can exercise their autonomy by choosing not to read that information. Let us look at some reasons why the individuals might opt-out of the information process. Some may have a genuine belief that the research project has great worth and want to participate, no matter how onerous the study or the potential risks of participation. Others may have been asked to participate by a trusted doctor and have enough faith in that doctor to feel assured that they will not be put at risk by participating. While the study doctor may be assured that the risk to the individual would be minimal, they could be unaware of personal circumstances where participation would be contrary to the beliefs of the individual. For example, the participant could be of a faith that does not eat meat and may be unaware that the study medication is presented in gelatine based capsules. While participation will not cause any physical harm, the individual may be psychologically distressed. Had the individual read the information themselves, they would have been aware of this and declined to participate. I would agree with Steiner that individuals should not be permitted to reject information, not because this could lead them to be taken advantage of by doctors, but because without information they will not know what is required of them. For example the trial medication may require the individual to avoid strong sunlight, as it has the potential to cause painful rashes. The participant may have booked a holiday in a sunny

country where he plans to participate in outdoor sports. Within two days of starting his holiday he develops a rash caused by the interaction between the sun and the trial medication, forcing him to remain indoors. This could have been avoided had he chosen to read the PIS.

Limitations of the current system

As we have seen, one of the disadvantages of the PIS is that some prospective participants don't fully read it, even if it is presented in lay terms. Sections describing the commitment of participants are often skimmed over. Depending on the nature of the clinical trial, they may need to make several visits to the hospital or trial site. Some visits can last several hours; they may have to undergo blood tests, have x-rays and may have to fast on several visits. If they are frail or infirm, attending all the required visits can be difficult; some individuals may have problems with mobility and need to be accompanied to hospital. In this situation, the support of a relative or friend is vital to their ability to participate. Therefore, the PIS should clearly outline both the risks of participating and any potential inconvenience this may cause. Attending clinic visits can also prove challenging for patients who are working. I was involved in recruiting individuals to a clinical trial which required medication to be taken before bed. On a study visit, one of the participants reported missing several doses of trial medication. When asked why he was having difficulty, he disclosed that he worked shifts, alternating a week of days with a week of nights. While he was aware from the PIS that he was required to take the study medication at specific times, he had not really taken his shift pattern into account when agreeing to participate. The

researcher cannot be expected to have in-depth knowledge of the lifestyle of each prospective participant, and can only hope that the individual will be able comprehend what impact participation may have to them.

I have discussed the different types of PIS. No matter what format is used, some individuals still seem unable understand what they have read. There may be several reasons for this, one being therapeutic misconception. The term 'therapeutic misconception' originated with Appelbaum (1982). It is defined as 'patients believing that clinical trials are designed to benefit those who enrol in them'. The aim of research and clinical care differ in that clinical care intends to treat the patient while research seeks to answer specific questions. Participants in clinical trial may benefit, but any improvements are secondary to the research question. De Melo-Martin (2008) found that therapeutic misconception was greatest in trials where the researcher was also the patient's physician. Despite having been clearly informed that they may not benefit from participation, trial participants felt sure that their doctor would not ask them to enter if they would not benefit from doing so. I think this is an understandable assumption. The General Medical Council (2010) guidelines require doctors to 'protect and promote the health of patients and the public'. It is not therefore unreasonable for patients to expect their doctor to act in their best interest. As most researchers in HIV clinical trials are also participant's clinicians, therapeutic misconception may be a real concern. In the UK, HIV care is generally provided in specialist units. These tend to be based in major cities, with patients living in rural areas having to travel long distances to attend clinics. BHIVA (2005) found that

seventy percent of patients remained with the same unit where they were diagnosed. The reasons listed included confidence in the skill of medical staff, friendliness of staff and that they felt assured that their confidentiality would be maintained. Their doctor will already have discussed HIV treatment with them, and will be aware of any problems they have experienced over the years. A relationship of trust will have been established, where the patient is confident that the doctor would act in their best interest with regard to their treatment and care. It can then be very difficult for the patient to accept that the doctor, in his research role, would ask them to consider participating in a clinical trial which may not be of benefit to them. They may believe that the doctor has inside information about the trial and is not permitted to tell them that the proposed new drug is better than the treatment they are already taking. While their doctor is able to assure them that the trial will be conducted as safely as possible and the possibility of harm has been minimized, he cannot offer assurances that the proposed regimen may be beneficial to them. The researcher themselves will be in a state of equipoise regarding the study medication; the evidence available to them may suggest that the treatment could be beneficial, but they will not know for certain until the trial is completed. The difficulty for the researcher is convincing the participant that they don't know if the study HAART will be better than the treatment they are already taking. Should anything untoward occur during the clinical trial the patient may blame the doctor, believing that he/she could have prevented any harm. This in turn could jeopardize the future doctor/patient relationship. Clinicians who are involved in research need to be aware of therapeutic misconception and take particular care when discussing clinical trials with their own patients. They should

reiterate that they themselves do not know if the trial medication will benefit the individual, or if they will experience side effects as a result of the trial medication. They could at this point restate the process for informing staff of side effects, which might strengthen this statement. If at all possible, it would be advisable for the clinician to avoid recruiting their patients to trials, and appoint another member of the research team instead. However, this may be difficult in smaller clinics or where the trial is seeking to answer a specific clinical question where the clinician is regarded as a specialist.

Another possible reason for individuals failing to understand clinical trials may be the way in which they are presented. Moss (2002) suggests that information about clinical trials is heavily weighted in favour of the potential benefits of participation, which patients may find misleading. This may be true to some extent, as one only has to look at information about clinical trials available on patient web sites to see that they are generally optimistic. Sites, such as ClinicalTrials.gov contain information about HIV clinical trials. These web sites include inclusion and exclusion criteria - an optimistic description of the trial but no information about potential side effects of participating. However, if an individual is interested in participating they are directed to contact a researcher. At this point, they will be given a PIS and so will have an opportunity to discuss the trial in more detail. The researcher should outline both the advantages and disadvantages of participation, including any side effects. However, the individual may be focused on the positive information he read initially and pay little heed to what he has been told. HIV positive individuals also discuss clinical trials on

web based forums. These sites have little or no input from clinicians or pharmaceutical companies. The information posted can be inaccurate and misleading.

Dawson (2009) suggests that while there may be a failure on the part of researchers to provide patient friendly information which can be easily understood, it is more likely that the failure to understand clinical trials reflects the human ability to comprehend certain types of information. He states 'The fact that a significant number of participants do not understand is not just a rogue result from a single study, but the persistent finding of numerous studies'. He goes on to suggest that if it is impossible to obtain informed consent, it makes no sense to require it. Dawson's claims are in part supported by others. Stead (2005) interviewed a group of patients who had participated in a randomised controlled trial on diabetes. They had met with the researcher, who was also their clinician, in a Glasgow hospital. The participants had been given a PIS, which contained the requisite elements and had been approved by a REC, and were given over twenty-four hours to read it. This was followed by a discussion with the researcher, who answered any further questions. When questioned after the interview, the researcher was assured that the participants had been given enough information to enable them to give informed consent. This view was in sharp contrast with the opinion of the trial participants. Most of the group complained that the PIS was very difficult to understand. One patient quoted... *'The first paragraphs a disaster. 'A randomised, double-blind study to compare the durability.....' Hello, hello-it's English I speak!'* They felt that the information sheet was

written in technical terms, which they did not comprehend. Many of the participants also had difficulty with the concept of randomisation. The participants were informed that they would be assigned to one of three arms. One group would receive the study drug, the next continue with standard treatment and the final group would receive a placebo. They were also told that neither they nor the doctor would know who was in which group. Despite reading about this in the PIS and having had the information verbally from the doctor, many of the group continued to believe that they would receive active treatment and that their doctor would know which arm of the trial they were assigned to.

The patients also had difficulty with the concept of equipoise. Even though they had been informed that the trial was comparing a new treatment for diabetes with standard therapy, and that there was not enough data yet to prove that the new treatment worked, most of the potential participants assumed that the new treatment must be better than the established treatment. The use of placebos was also not well understood. The participants were aware that a placebo was a 'dummy drug', and had been informed some of the patients would be given a placebo for a short while. They were informed that patients would be closely monitored and offered 'rescue therapy' if their blood sugar became too high. Despite this information, most of the group displayed a therapeutic misconception believing that they would receive active treatment while on the trial. They were very upset when they learned that they may have not been given active treatment, as they felt that it was the duty of the doctor to heal. By not ensuring that they were in the active arm of the trial, they felt as if the

doctor had failed in his/her duty. The majority of the trial participants felt that the researcher, who was also their clinician, would not have asked them to consider participating in the trial if there was any possibility that they would not benefit from it. They went on to say that the experience of research would have a negative impact on their future dealings with health care professionals, as they could not trust their doctor. Stead concluded 'The consent of these people gave must have been 'informed', but the information was certainly not comprehended'. Kenyon (2004) also found a lack of understanding in women who had participated in a gynaecological trial. Individuals were asked to complete questionnaires following participation to establish what they believed were the aims and objectives of the trial. While the PIS was highly valued as a source of information, the participant's interpretation of information did not reflect the true nature of the study. Poor recall of trial information was seen in fourteen percent of responses. While these studies had very different aims and were conducted in different locations, the issues raised by participants are very similar. Researchers felt that they had fulfilled their obligation by providing information sheets and discussing the trial, and were satisfied that the participants had understood enough to give informed consent. This is in contrast with the views held by the participants who found the PIS difficult to understand, and had not fully understood the explanation given by researchers.

The basic elements of informed consent outlined by the International Conference on Harmonization (ICH) guideline for good clinical practice (1996) focuses on the provision of information on the clinical trial for the prospective participant. The World

Health Organization (1993) guidelines go a little further, requiring the researcher to seek consent only if they are satisfied that 'they (the subjects) have adequate knowledge of the facts'. No mention is made as to how the researcher might establish that the 'subject' has this knowledge, or what constitutes 'adequate knowledge'. While the lack of understanding will not affect the results of the trial, can researchers truly be seen to respect the autonomy of the individual if they don't ensure that participants understand the information they have been given? Beauchamp and Childress (2001) state that for informed consent to be morally satisfactory the individual needs to demonstrate competence by understanding the provision of information and then making a decision based on that understanding. They suggest that while it may be unreasonable to fully inform an individual in some circumstances - such as complex medical procedures - it is possible to ensure that individuals are adequately informed in order for them to make an informed choice. We have seen that the provision of the PIS alone may not be sufficient to provide information about trials. While I would agree with Dawson that participants have difficulty understanding PIS, I would disagree that this justifies removing the requirement to seek informed consent. I believe that there must be a more effective way of communicating information. Individuals have the capacity to understand complex information and act upon it. For example, we have seen a rapid expansion in the communications industry. Items such as internet enabled telephones and digital books are common place. The instructions that come with these items are often very complex, yet most people have no difficulty understanding how to use them. How does the way in which we process this information differ from information given in a PIS? Certainly, some of the

concepts found in the PIS - such as the use of placebos - are not common in technology. However, some aspects of new technology can be just as challenging. We need to look at how people learn and understand, and apply this knowledge to developing new and more effective methods of communicating trial information.

Can we improve the information giving process?

If we agree that the provision of the PIS alone is not enough to engender understanding about a clinical trial, what steps can we take to improve understanding using the tools already at our disposal? Current practice requires researchers to discuss the proposed trial with potential participants and answer any questions they might have following the provision of a PIS. This is often viewed by researchers as a formality prior to obtaining consent, and they may not spend enough time with the individual to check if they had understood the trial. Katz (1984) was concerned that the provision of information, as outlined above, did not facilitate understanding. As such, he trialled a model based on conversation where informed consent was viewed as a mutual and participatory process. The individual was encouraged to ask questions and share ideas with the person taking consent. This enabled the person taking consent to have a clearer understanding of the participant's understanding and how involved they wanted to be in the process. Brody (1999) further developed this conversational model of consent, where the researcher spoke with the client, not to them. In this model the process of obtaining consent is part of an on-going dialogue with the individual. It encourages them to ask questions, which they may have felt self-conscious about raising in the traditional consent process. It also encourages

them to change their mind should they realise that participating does not meet their expectations. Participants are much more involved in the research process and are likely to have greater understanding about the trial and what it means to them than those consented by the standard method. They may feel more motivated to follow all the requirements of participation, such as attending clinic visits, if they are better informed of the importance this has on the outcome of the study.

Bhopal (2008) looked at ethical codes for undertaking research with ethnic minority populations. He began by hypothesising that research with ethnic minority groups could be problematic due to cultural and language differences. He states that while it is not practical to create separate codes for all ethnic minority groups, researchers need to consider potential influences which might require a different approach to research. He felt that this approach could include arranging for information to be translated into appropriate languages, or to arrange same sex interviewers. He argues that in order to offer a fair and just approach to research all research participants should be treated equally. I strongly support his hypothesis. Cultural practices can affect research, and prior knowledge can be invaluable in overcoming potential problems. For example, when I first started working as a researcher with the African community, I could be waiting for up to an hour for participants to arrive. I finally asked a colleague, who is from Uganda, for advice. When she had stopped laughing, she explained that in Africa people generally had a much more relaxed attitude to time keeping. I was already aware of this having lived in Africa for many years, but had not applied this knowledge to my clinical work. While a relaxed attitude

to time may only be an inconvenience in a clinical setting, the research setting is quite different. Blood samples in the trial had to be collected at specific times as they were collected by a courier and shipped to a central laboratory. She suggested that I approach time keeping in a different way. When scheduling their next appointment, she suggested that I should ask participants if they would be keeping British or African time. I was initially quite concerned about taking this approach, feeling that they would think that I was being rude and insensitive. However, all of the participants were very amused by the question, some asking if I had been given inside information into African time-keeping! I was able to use this opportunity to inform them why time keeping was important during the study. Time keeping did improve, but so too did my clinical practice. I arranged for appointments to be half an hour earlier than they were scheduled which meant that even if participants were late, I still had time to get the blood couriered to the lab on time. Had I taken into consideration the cultural differences around time keeping prior to recruiting, I would have been less anxious and more able to deal with late appointments. I have taken this lesson into consideration and now always include a section on why time keeping is important when I am writing participant information sheets. Cultural aspects play a significant role when conducting research.

Hill (2006) held focus groups with African women, asking for their input in designing a PIS and consent form which would be readily understood by them. The tool which they developed was very different to the guidelines provided by NRES. It involved the use of metaphors to explain complex concepts and the use of visual aids. The groups

felt that it was important to provide information in small portions over multiple visits, where the individual has time to discuss the research in a relaxed setting, and have any questions answered prior to giving consent. This is in contrast to the current method where provision of information and consent is completed in two visits. The groups also felt that it was important for researchers to have a good understanding of the cultural background of the prospective participants, in order to contextualise questions.

While the conversational method described by Hill would certainly ensure that information is provided in a culturally acceptable manner, it is likely that there would be resistance from researchers in the UK setting. Multiple visits would require them to spend much longer with participants, which may not be possible if they have clinical commitments. Conversational methods of information giving may be more difficult to use with individuals who do not have English as a first language, such as HIV positive asylum seekers and refugees. However, some HIV researchers in the UK are beginning to look at different ways of imparting trial information to ethnic minority groups. While these practices are not yet wide spread they are proving to be effective. One method which has proven successful builds on the close relationships developed by clinics and community support groups. African HIV community groups have arranged for clinicians to be present on specific trials which their members have expressed an interest at an informal community event. It was agreed that the clinician would present at the end of the meeting, following the support group but after food. This timing allowed those who did not want to ask questions themselves to pass on

their questions to the chairperson. It was also established that this was not to be viewed as a recruitment opportunity by the clinician. Those who wanted further information about the trial/were interested in participating could collect a PIS at the end of the session and contact the researcher at a later date. Participants have reported that they have benefited from this format. They felt more likely to ask questions about trials in this type of setting without feeling that they had to commit to participate. They also felt supported to ask questions by their peers. The clinicians also found the experience useful. Apart from gaining an insight into concerns voiced by the community, they also found the social setting helped to further their understanding of African culture, including the cuisine. This is an adaptation of the conversation method discussed by the participants in Hill's focus group. While it does not involve multiple information giving sessions, it does allow potential participants the opportunity to ask questions which they may not feel able to do in a one-to-one setting. This may result in a better understanding for the individual on what participation would entail, enabling them to make an informed choice. However, concerns still remain about lack of comprehension if the individual does not have English as a first language. Both groups suggested that the use of visual aids such as CDs and DVDs could be used to provide information to individuals who cannot read or understand English. While it may be impractical to have written translations of all documents, provision of information in an oral format can be tailored for the individual. Recordings could be made of the information given to the participant by the researcher during the initial trial visit translated by the interpreter. This would be dependent on the researcher having access to recording materials and the participant

having the necessary equipment to view the information. The use of conversation methods to convey trial information should be used as a supplement to enhance understanding of the clinical trial, but should be supported with a PIS.

We have seen that both conversational and PIS methods of providing information may be hampered by the individuals lack of understanding of English, or the researchers lack of other languages. While the individual's level of English may be sufficient for day to day use, it may be insufficient to understand trial information. In order to overcome language difficulties researchers may utilize the services of interpreters. If an interpreter is to be used, they should be an accredited translator, holding the Institute of Linguists' Diploma in Public Service Interpreting or a similar qualification. Interpreters should also be aware of the need for confidentiality, and have signed a contract to that effect. While interpreters employed by the NHS are bound by the same confidentiality as all other NHS employees, trial participants may still be concerned that they will relay their HIV status to their community. This is of particular concern if the individual comes from a minority group where there is a strong possibility that they will be known to the interpreter. As well as concerns about individual confidentiality, it can be difficult for prospective volunteers to deal with the interpreter's response to their HIV status. I have had interpreters decline to translate as they have recognized the name of a family member and felt that it would not be in either of their interests if they were to identify themselves to a relative.

Researchers themselves may need to be trained to work with translators. Phelan

(2003) suggested that doctors often give a long, technical explanation to interpreters and expect them to impart this information to patients. In clinical research, this can be particularly difficult, when patients need to have a clear understanding in order to make an informed choice. It may be useful for researchers to develop a closer working relationship with the organizations which are tasked to provide interpreters. The researcher and organization could work together to develop a training package for interpreters - giving an overview as to the aims and objectives of clinical trials. This would help to ensure that interpreters have a greater understanding of research and understand the need to providing an accurate translation of patient information. It may also be useful to use the same interpreter throughout the trial. This will both reduce the need for the researchers to have to explain a specific trial to a range of individuals as well as allaying any concerns the participant may have of disclosing personal details to a range of individuals.

Some prospective trial participants bring a relative with them to translate. This practice is discouraged for many reasons. In HIV trials, it is easy to assume that the relative is aware of the individual's status if they have been brought to translate by the patient/research participant. However, this is not always the case. One of my colleagues was placed in the unenviable position of having a relative interpret the PIS for an HIV trial only to be asked 'So, is my relative HIV positive'? The patient thought that it would be an ideal opportunity to inform their relative of that they were HIV positive. This was not a view shared by either the researcher or the relative, who were both quite upset by the experience. Even if the relative who is translating is fully

aware of the health status of the prospective participant, their level of English may not be sufficient to translate and understand the PIS. Breen (1999) found that twenty-three–fifty-two percent of adhoc interpreters misinterpreted words or phrases. This is a real concern in the research setting, where understanding is necessary prior to giving consent. If participants are not given the correct information on which to base their decision to participate, any consent given would be void. The relative may also have strong views on trials and may translate the information in such a way as to influence the individual's decision to participate. For these reasons, it is generally agreed that if the information cannot be provided in the patient's native tongue or a neutral translator be provided, the individual should be excluded from participation. While this could hamper recruitment to clinical trials, it is better than recruiting individuals who may not have sufficient understanding of the information to give informed consent.

A useful alternative to face-to-face interpretation is the use of telephone translation services, such as Language Line. This service is widely used in NHS premises and by some of the larger HIV charities. This form of interpretation can be very useful for individuals who are concerned about confidentiality as the interpreter is not visible to the prospective volunteer. However, this service has its limitations. Unlike conventional interpretation services where an interpreter is booked for a specific time, telephone interpreting is dependent on having an interpreter on hand who speaks the required language. It may be time consuming in a clinical trial setting waiting for an interpreter to be found. It can also be problematic passing the phone from person to

person if there is not a hands free telephone available. This may also break-up the spontaneity of the discussion, and some important aspects can be missed.

Having given the participant information about the trial can researchers be sure that they have understood it? The answer to this must be no. Some researchers try to overcome this by asking participants to recount a brief outline of the trial. While this may give the researcher an insight into the participant understanding, it cannot comprehensively cover all aspects of the trial. Stead (2005) suggests another way to check understanding would be to pilot the PIS within the target population and follow that with a questionnaire. This would enable the researcher to identify any recurring problems of understanding and perception and modify the text as necessary prior to submitting it for ethical approval. This is supported by NRES (2011) who recommend the involvement of patient groups in research. However, having the PIS proof read by the target population does not guarantee that it will be understood by an individual participant. Is it possible to check participants understanding? Ames (2008) suggests that the participant should be given the PIS to read, which is then followed by a short multiple choice questionnaire to assess their understanding. Depending on the answers they have given, the researcher should provide a more detailed explanation on those aspects which needed clarity. While I think that Ames suggestion has some merit in that researchers spend more time discussing the trial, my overall opinion is that it would deter individuals from participating. Few people enjoy examinations and this method, for some, would feel like being back at school. It would also be of little use to participants who did not have a good understanding of written English, such as

HIV positive asylum seekers and refugees, excluding them from a process which they wished to participate in. It is also likely that this method would require additional or longer visits to the clinic, which could also act as a deterrent. However, I do accept that researchers need some method to ensure that participants have a basic understanding of any trial. Unlike Ames, I do not feel that it is necessary for prospective participants to complete a questionnaire to check their understanding. Nor do I think it is necessary for prospective participants to make numerous visits to see the researcher prior to commencing the trial. It is current good practice for researchers to take time to discuss the PIS with prospective participants and address any concerns they may have. It is not enough to ask the individual 'Have you read the information sheet? Do you have any questions? Good, sign on the dotted line'. This happens all too often. The individual is often discouraged from asking questions, and can feel foolish if they do so. The information giving process should comprise of open questions about the main aspects of the trial. These open questions should be designed to facilitate a two way conversation between the researcher and prospective participant, but not give the individual the impression that they are being interrogated. During this process, the researcher can correct any misconceptions about the trial and encourage the individual to ask any questions which they might have. Some may have difficulty understanding concepts such as randomisation, equipoise and placebos. The researcher may need to work with patient groups to deliver this information in language which can be easily understood by prospective participants. When discussing the trial, the researcher will need to take into account that the prospective participant may have difficulty articulating the aims and objectives of the

trial. This may in part be due to language difficulties, but may also reflect their educational background. While individuals may not be able to give a technical explanation of the study, they should be able to demonstrate that they have understood the risks and benefits of participating and be aware how participation could impact their daily activities.

There may be resistance from researchers to change. Some may be concerned that they do not have the skills to use conversational methods and would need additional support and training. Others may opt to delegate consent taking to another member of the research team who is more skilled in communication. It is of no concern which member of the research team undertakes this task, as long as they are able to communicate in an effective manner. Some might argue that they do not have time to spend away from their clinics. Others may be concerned that better information may result in a reduction in the number of participants; after being fully informed of their obligations some individuals could decide this is not for them. While these points are valid, the additional methods of providing information provide an opportunity to discuss the trial with a large number of individuals. They may in turn discuss the study with others, thereby increasing the number of potential participants. Better informed participants will be aware of any burdens associated with the trial and may be less likely to drop out at a later date. Further research would be needed to support the claim that these additional methods do indeed increase recruitment and retention to trials. We have seen the standard process does not always convey information. In order to ensure that consent is informed, the research community may need to re-

think how information is provided to trial participants in general - and HIV positive asylum seekers and refugees in particular.

Conclusion

In this chapter I have argued that the current methods of providing information to HIV positive asylum seekers and refugees is not effective. No matter what their background, those participating in clinical trials appear to have difficulty understanding the information they have been given. Their lack of understanding could be based on inadequate provision of information, how the information was imparted or - as Dawson says - people just don't understand. Possibly, it is a combination of all three. Two questions remain. Should researchers permit individuals to participate in clinical trials where there is doubt that they have understood information they have been given, and if they do so can they be said to be respecting that individual's autonomy? Furthermore, having agreed to participate when they do not fully understand a trial, can the individual really have been said to have given informed consent?

I will start by addressing the first question. It is very difficult for researchers to measure exactly how much information an individual has retained. The individual could have understood but been unable to articulate that understanding. They may appear to have understood, but have missed pertinent information. Researchers should be able to clearly demonstrate that they have taken every practical step to explain the clinical trial to the individual, taking into consideration cultural factors. However, I would argue that if there are any doubts about understanding, researchers

should weigh up the potential harm the participation may incur as a result of participation. In trials which carry minimal risk, such as where participants have to complete a questionnaire and give a blood sample, the individual is unlikely to come to any harm even if they cannot fully demonstrate understanding to the researcher's satisfaction. For more complex trials, the risk to the individual would be much higher. For example, participants may agree to a lumbar puncture having failed to understand that this is likely to be painful. If there is a risk of harm and the participant demonstrates a lack of understanding, they should not be permitted to participate. Some would argue against this stating that the individual has a right to self-determination. In daily life we certainly have the right to make choices based on information which we have misunderstood. I would argue that this is different in the clinical trials setting. Even if the participant agrees to a procedure without fully understanding it, the researcher still has a duty of care to ensure that the patients are not harmed by participation. If he were to recruit a participant and then subject them to a procedure that had not been understood, resulting in pain or discomfort, they would be failing in that duty.

I will now look at the second question of informed consent. Participants do not need to be aware of every nuance of the trial, but should be able to demonstrate a basic understanding. As we have seen earlier, it is always possible to add additional information. I would argue that the participant should - at minimum - know what participation in the trial would mean for them. This includes any risks and benefits and how much time they will need to dedicate to participation. If they cannot demonstrate

this basic information, any consent they give will certainly not be informed.

We have looked at different methods to communicate trial information. NRES (2011) provides comprehensive guidance for researchers to support them in designing information sheets. Despite these guidelines, PIS are often written in very technical terms which are meaningless to the target population. This is of particular concern where clinical trials involve HIV positive asylum seekers and refugees. While many will be able to understand spoken English, they may have difficulty reading and understanding the PIS. The NRES guidelines (2011) state that 'providing an information sheet is just one part of seeking consent'. Despite this, NRES provides little guidance to researchers or RECs on what these additional methods might be. There is also no guidance on how these methods could be presented to the REC. For example, the REC I sit on was asked to review a particularly complex clinical trial. The researcher had included a very long PIS which attempted to describe the trial, but which many members of the REC had difficulty understanding. The researcher attended the committee meeting where he was asked to clarify exactly what was expected of the participant. He produced a flip chart and equipment and went on to give a very clear and entertaining demonstration on the use of the medical device under investigation and the impact this would have on the participant. He explained his team used this method to impart information to patients in a clinical setting, and planned to do so for prospective participants in the trial. When he was asked why he had not included this in the PIS, he stated that there was no place to describe the demonstration in the ethics submission. This outlines the challenges researchers face

when they wish to utilize additional methods of providing information. If we are to give weight to the findings of Hill (2006), the use of demonstrations may be more acceptable and effective when describing clinics to individuals from sub-Saharan Africa, including HIV positive asylum seekers and refugees. Therefore researchers planning to conduct research with this population should be supported to utilize innovative methods of information giving.

The role of the REC is pivotal to the information giving process. As part of their role, they review PIS to ensure that it reflects the trial protocol and provides enough information to enable the individual to make an informed choice. Researchers are required to make changes to the PIS prior to gaining approval for the trial. While the subsequent draft is generally improved, it may still be lacking in clarity. These 'improved' information sheets are often approved as RECs may be reluctant to delay the clinical trial due to pressure from NRES. In order to improve provision of information, RECs need to be more open to novel and innovative methods, whilst ensuring that individuals have enough information to make an informed choice. RECs should support researchers to be more creative in the provision of trial information, especially for individuals who have language or cultural needs. While this will be challenging and would need support from NRES, it would improve the provision of information. Unless improvements are made it is likely that information given to participants in clinical trials will remain a written exercise, used to tick regulatory boxes but not really support understanding.

Chapter 7

Consent -Vulnerability and voluntariness

Being HIV positive alone may not increase an individual's vulnerability in the research setting. For example, one of my patients is a solicitor in full-time employment. He has his own home, a long-term partner and good social support. While being HIV positive may make him vulnerable in some aspects of his life, his decision to participate in an HIV clinical trial was based on a desire to contribute towards the development of future treatment. In contrast, another patient is a Sudanese refugee who is appealing to remain in the UK on compassionate grounds. He is not permitted to work, is dependent on benefits and lives in a hostel with little support. While he did not really want to enrol in the trial, he felt that participation would give weight to his asylum claim. While both these patients are HIV positive, the Sudanese patient is more vulnerable in the research setting due to his asylum status.

In the previous chapter I looked at the issue of providing information in a way which enables the individual to understand the proposed trial and thereby give informed consent to participate in it. Once the researcher has ensured that the individual has understood the aims of the clinical trial and is aware of any risks and benefits of participating, can they then go on to assume that the individual is in a position to give informed consent to participate? The answer to that is no. In order to give valid consent, the individual needs to have information on which to base their decision, to be competent to make that decision, and give their consent voluntarily. Whilst poor information undermines voluntariness, there are other factors which can influence the

individual's decision to give informed consent. This chapter seeks to address some of the issues which are specific to HIV positive asylum seekers and refugees participating in clinical trials in the UK.

In this chapter I will begin by discussing the role of vulnerability in the research setting. Some researchers do not consider that HIV positive individuals are more vulnerable than any other research participant. I will argue against this view and outline areas which may increase their vulnerability in the research setting. I will go on to argue that while they may be more vulnerable, they should not be excluded from research provided that steps are taken to minimise the increased risk. In the second half of the chapter I will discuss the role of ethics committees in protecting those considered vulnerable, and look at ways in which ethics committees could be more proactive in research involving HIV positive asylum seekers and refugees.

While all individuals are vulnerable to some degree when participating in clinical trials, some individuals may be more vulnerable than others. Traditionally groups such as prisoners, children, etc. are considered vulnerable by NRES. If a researcher intends to conduct research on these populations, he is first required to justify why the research cannot be conducted with another study population. For example, researchers will only be able to establish the efficacy of antiretrovirals in children by conducting trials in HIV positive children. If the REC accepts that the use of a vulnerable population is justified, the researcher then has to outline the measures which he intends to take to protect the individual's autonomy, protect them from harm,

and protect them from exploitation.

Who is vulnerable in research?

While researchers are required to protect the vulnerable in the research setting, there is no consensus on who is to be considered vulnerable. For example, the Declaration of Helsinki (2008) outlines in detail measures researchers are required to take to protect vulnerable research subjects without providing a definition of those considered to be vulnerable. The Council for International Organizations of Medical Sciences (CIOMS 2002) does provide researchers with a definition of those who may be considered vulnerable. These include 'those who are relatively (or absolutely) incapable of protecting their own interests because they may have insufficient power, intelligence, education, resources, strength or other needed attributes to protect their own interests'. While this definition clearly outlines the attributes of the individual, it may not be very helpful for researchers who are tasked with identifying a vulnerable population. For example, it would be unlikely that all participants in the trial lack intelligence. Identifying specific groups who may be more vulnerable may be easier than looking at individual characteristics.

The International Conference on Harmonisation Good Clinical Practice (ICHGCP 1996) guidelines expands the list of those considered vulnerable to include those within a hierarchical setting. Their guidelines state:

Individuals whose willingness to volunteer in a clinical trial may be unduly

influenced by the expectation, whether justified or not, of benefits associated with participation; or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, and persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors and those incapable of giving consent.

The ICHGCP guidelines reflect the requirement of NRES for researchers to justify the inclusion of vulnerable individuals and, if they are selected, what means will be applied to protect their rights and welfare. Unlike the NRES guidelines, the ICHGCP identify refugees as a vulnerable group.

I am now going to look at some of the varying accounts of vulnerability and highlight some of the common themes.

Leight (2003) defines vulnerable populations as social groups who have increased susceptibility due to adverse health outcomes. These groups are less likely to have access to health resources, and be at greater risk than the general population. Her

definition is supported by Reeder who also highlights that the lack of access to health care increases the vulnerability of the individual. I agree with both writers. Those of us fortunate to have access to NHS treatment do not worry about becoming unwell, knowing that we will be able to access medical care should we need it. Those who do not have access to this service worry about what will become of them should they need this care and be unable to pay for it. While antiretroviral medication is now available for HIV positive asylum seekers and refugees, they can still be charged for any other health related illness. As such, the fear of becoming unwell is very real to this population.

Kottow (2003) discusses the difference between vulnerability and susceptibility. He states that all human beings are vulnerable and as such we should all be afforded the same protection in research ethics. He suggests that the principle of justice should offer protection to all who are 'vulnerable' i.e. all human beings, while those who are 'susceptible' need a specific intervention. This feels to me very much like vulnerability under a different name. Kottow offers a list of criteria to distinguish those who are predisposed to additional harm. These include the poor, undernourished or those lacking in medical care. He suggests that labelling individuals as vulnerable is misleading. He prefers the term susceptible. He offers a definition of vulnerable as being intact but fragile, while susceptible suggests injured and predisposed to additional harm. He suggests that having an awareness of the difference between those who are vulnerable and those who are susceptible should help to remove the double standards in research ethics. He states that if the term vulnerable is replaced by susceptible, it would offer more protection to those who are already

disadvantaged. I disagree with Kottow for a number of reasons. Those considered vulnerable in the research setting at the moment tend to belong to specific groups, such as children and prisoners; the individual characteristics of that person are not taken into consideration. Firstly, and on a pragmatic level, identifying individuals who are susceptible to additional harm through poverty, lack of food or medical care may be very difficult in the research setting. Researchers are unlikely to want to ask questions which are, for many of us, of a sensitive and personal nature. While asking these questions on an individual basis would enable researchers to take each person's circumstances into consideration, what they do with that information is difficult. Would they have to say to the person; 'I'm sorry you can't participate, you are too poor?' This might further increase the isolation felt by that individual, whose decision to participate may have been based on an altruistic desire to help. While the system we have in place at the moment is not perfect, it does allow researchers to identify vulnerable populations and identify measures they plan to take to protect that group. Reimbursement of travel to all participants will enable less wealthy individuals to attend appointment and not be out of pocket. Secondly, Kottow suggests that labelling those who are poor, undernourished or lacking in medical care as susceptible will somehow afford them special protection. This is no different than the present system where vulnerable populations are identified and researchers initiate measures to protect them. I find it difficult to see how labelling individuals as 'susceptible' could afford additional protection to those in need. Accepting that there are individuals whose particular circumstances may increase their risk in clinical trials; would it not be more effective to raise the standard of care for all clinical trials

participants, so that all are afforded a high standard of care, no matter what their risk? This would reduce the need for labelling and the possibility of stigmatising those already disadvantaged, and would ensure that those who want to participate in clinical trial are supported to do so.

Levine (2004) argues that the concept of vulnerability is both too broad and too narrow. By too broad, she suggests that so many groups in research are now considered vulnerable that the concept of vulnerability has lost its force. She suggests that being labelled as vulnerable only offers limited protection. In contrast to Kottow, she argues that by focusing on group characteristics of vulnerability, we are in danger of overlooking other factors which put research participants at risk of physical harm, such as flawed trial design. She goes on to argue that defining all members of a group as vulnerable does not take into account the individual characteristics of the members of that group. She argues that people can be vulnerable in some situations, but not in others. She suggests that all those involved in research should develop a standard tool to identify the vulnerable. This will enable the research community to provide a more targeted form of protection. I agree with Levine to some extent. Firstly, by nature of participating in trials most participants are to some extent vulnerable. They are exposed to new drugs, procedures and processes which may - to some degree - render the individual vulnerable to harm. The term vulnerable should only be applied to those who are at increased risk from participation over and above the background risk. I also agree that defining all members of a group as vulnerable does not take into consideration the individual characteristics. For example, those recruited

to HIV clinical trials will all be HIV positive. However some participants will be in full-time employment, have English as a first language and have agreed to participate for altruistic reasons. In contrast, other HIV positive participants may be refugees, have little English and have enrolled in the trial in the hope that it will positively influence the outcome of any asylum application. While both groups may be vulnerable due to their medical condition, those in the former group have additional characteristics which increase their vulnerability in the research setting. Finally, Levine suggests that researchers should get together to develop a tool to identify the vulnerable. This may have some merit, but it is difficult to see how this would work in practice. As we have seen, researchers have very differing views on what constitutes vulnerability in the research setting.

Kipnis (2004) argues that individuals are vulnerable in the research setting if they have a medical condition for which there is no known cure. He suggests that researchers choose these patients for research due to their vulnerability as they may be willing to undergo risks that other research participants would not, due to the fact that they have no other option. He argues that research with individuals who have a terminal illness where there is no safe effective treatment can be acceptable, provided that they are informed and aware that the treatment may not be effective. I agree that this group are vulnerable in the research setting for the reasons Kipnis outlines. Those with no viable treatment options may take risks in the hope of expanding their lifespan. I disagree that researchers target this group due to their vulnerability. While it is true that this group are vulnerable due to their medical

condition, Phase Two to Four trials require individuals who have the condition which may respond to the trial medication. The participant's vulnerability and medical conditions are intertwined; researchers have no choice but to recruit from this population. How does this relate to HIV treatment? HIV is now regarded as a chronic manageable condition. However, overtime the virus can become resistant to treatment. Those who have developed resistant strains of the virus will eventually succumb to opportunistic infections and die. For this group the only option to extend their lifespan is to participate in clinical trials involving new classes of antiretrovirals. These participants are vulnerable due to their medical condition but are recruited to trials because they have a resistant virus.

While it may be difficult to outline all the ways in which individuals may be vulnerable, I believe that a working definition for the purpose of research should include those who lack competence, have compromised voluntariness and have physical or psychological impairment. Using the above definition I will now go on to show how HIV positive asylum seekers - as a group - are vulnerable in the research setting and will argue that they should be considered as a vulnerable population by NRES.

Lack competence

When recruiting to a clinical trial, researchers must ensure, (as far as possible) that the prospective participant is competent to consent. They may not have sufficient English to understand the aims and objectives of the trial and the risk of participation, or they may lack capacity to consent. In chapter 6 I discussed measures which would

enable those with language problems to participate, including the translation of written materials, and the use of informed translators. I will now discuss those who lack capacity to consent. The Adults with Incapacity (Scotland) Act 2000, the Mental Capacity Act 2005 and the Medicines for Human Use (Clinical Trials) Regulations 2004 require that those without capacity should be involved in the decision to participate. Researchers should ensure that the content of trial information provided for these prospective participants can be understood by them. These PIS should be in a clear format and should include an overview about the trial as well as any risks and benefits of participation. Researchers also need to take additional time discussing the study with this group, answering any questions in lay terms. If there is any question that the participant does not have the capacity to consent, and the trial involves investigational medicinal products, the Medicines for Human Use (Clinical Trial) Regulations 2004 requires the investigator to seek consent from a legal representative. The legal representative is under no obligation to undertake this role if they do not wish to. Seeking consent from a legal representative may be problematic if the potential participant is HIV positive. In order to give informed consent the legal representative will be required to read the PIS, which will outline that the trial is seeking to recruit HIV positive participants to take part in a drug trial. The legal representative may not be aware of the HIV status of the prospective participant; thus breaching the individual's confidentiality. As we have seen earlier, those who are HIV positive still face stigma. Should the individual regain capacity, they could find themselves ostracised by their community. Some might argue that the potential harm caused by a breach in confidentiality outweighs the potential benefits of participation in

the clinical trial. However, there are some research questions which can only be answered by enrolling those who lack capacity. For example, Yanofski (2008) highlighted the need for further research looking at the interactions between antiretrovirals and antidepressant medications. Since this article was written, new classes of antiretrovirals have been licensed, which are necessary to treat drug resistant virus. Individuals who are developing drug resistance and are also being treated for depression may benefit from these drugs, but research will be needed to establish whether these new antiretrovirals are safe to take with antidepressants. Cohen (2009) also found higher levels of depression in HIV positive asylum seekers and refugees than both the general population and those who have HIV who are not asylum seekers and refugees. Clinical trials are needed to establish the safest and most effective of treating HIV positive individuals with depression. This type of trial will need to recruit depressed patients, some of whom may lack capacity or lose capacity during the trial should their mental health deteriorate. If researchers can justify the importance of conducting research with this population, I would suggest that there is a case for appointing an independent legal representative if the HIV status of the individuals is unknown to family and friends. It may be difficult to ask the family if they are aware of the individuals HIV status without breaching confidentiality as this is often kept a secret. However, it is standard practice in all HIV clinics to record who the patient has disclosed to. An independent legal representative could be appointed to consent in these situations.

Compromised voluntariness

I will now look at ways in which HIV positive asylum seekers and refugees may be vulnerable due to compromised voluntariness. For a decision to be considered voluntary, the individual should be free from undue influence. There are different forms of undue influence; coercion, perceived coercion, rational persuasion, manipulation and undue inducements. Our clinic works closely with a local HIV support organisation, where clinic staff give an update on new developments in HIV on a monthly basis. At the end of these sessions we have a question and answer session where members of the group pick a topic they want to discuss. On several occasions this has been around clinical trials. Many of the members of the support group have participated in trials, and the majority of those who have not have been asked to do so. One of the issues which have been discussed several times is recruitment to clinical trials. Members of the support group stated that they feel under pressure from medical staff to participate in clinical trials. This view is reflected by Nelson and Merz (2002) who believe that certain behaviours on the part of the researcher can persuade, manipulate or coerce potential research participants. The support group I have spoken with have given a number of reasons for this, which I will give examples of during this section.

I will begin by looking at coercion and perceived coercion and will use examples given by the support group to illustrate how this could influence the individual's decision to participate in a clinical trial. The Oxford Dictionary defines coercion as impelling or forcing into obedience. The individual does not have to give into this force, it is enough that they felt under pressure to comply. In its guidance document on good

clinical practice in clinical trials, the Institute of Clinical Research (1996) requires researchers to meet stringent criteria in the process of obtaining consent. In point 4.8.3 it expressly instructs investigators that “Neither the investigator, nor the trial staff, should coerce or unduly influence a participant to participate or continue to participate in a clinical trial.” As mentioned in the previous chapter, most HIV physicians are involved in clinical research, recruiting from patients who attend their clinics. As HIV treatment is life long and patients are seen on a regular basis, it is not unusual for doctors and patients to get to know each other over a number of years. Patients may be grateful for the care provided over the years and feel an obligation to enrol in a clinical trial as they perceive this as helping their doctor. Their cultural background can make it more difficult to refuse a request from someone perceived to have a high status. Most doctors who have experience working with clients from sub-Saharan Africa are aware of the power imbalance and will take that into consideration when discussing clinical trial. However, there are others who exploit their position to increase recruitment to a trial. For example; Dr A suggests that he might not have time to write a letter of support for patient B, but he might be able to make time if patient B was one of his special research patients. While patient B does not really want to participate, he does need the letter of support as his immigration appeal is due next week. As such, he reluctantly agrees to participate. The doctor has not said out-right that he would not write the letter. It may be that the doctor only meant that he would not be able to write the letter immediately and would eventually get round to writing it. However, the patient perceived that the letter would not be written *unless* he agreed to participate. Perceived coercion can be as detrimental to valid consent as

actual coercion. Patients might feel that despite the doctor's assurance that they will not be disadvantaged by declining to partake in a clinical trial, any refusal may jeopardise support for their staying in the UK. Even experienced researchers may be unaware that the way in which they ask patients to participate in a clinical trial can be open to misinterpretation. One member of the support group recounted that she had been asked to participate in a trial following a discussion with the doctor about her on going asylum appeal. She assumed that the offer to enrol was linked to the asylum appeal and agreed to participate thinking that it would support her application. Having worked with the doctor in question for several years, I asked her permission to discuss this with her. The doctor was horrified to think that the patient had linked her appeal with the trial, and arranged to discuss it with the patient at the earliest opportunity. The patient did decide to continue with the trial but was now very clear that it would not help her asylum claim. The doctor also resolved to be more careful about when she discussed clinical trials in the consultation. This outlines the need for those in a position of power to take care when discussing trials with asylum seekers and refugees.

The obvious solution to the problem of coercion or perceived coercion would be for doctors who have a dual role as researcher and clinician not to enrol their own patients in clinical trials. Indeed, this is the NRES 'gold standard'. However, this may not be practical for several reasons. In smaller units there is usually only one doctor who has responsibility for the clinical trial. If he is also responsible for the patient's care then the patient may have no choice but to see him. While most trials employ

research nurses who could discuss the trial with the participant, there may be aspects of the trial which will need to be discussed with the principal investigator, which is the doctor. In larger hospitals, HIV units can have several doctors who may be involved with the same trial. In this case, it may be possible for another medic to discuss the trial and take consent. If the patients' doctor is the only one who can consent, and the patient is keen on participating, he may suggest that the patient attend another unit for study visits. This too may be problematic. There may not be another hospital involved in the same trial within easy travelling distance. The prospective participant may be reluctant to travel long distances, especially if the trial involves numerous study visits. Additionally, it may have taken the prospective participant some time to overcome their fear of stigma and discrimination and to build up a trusting relationship with medical staff. They may be reluctant to see someone else or be concerned that they might encounter someone they know in a new hospital and have to explain why they are there.

Another form of undue influence is manipulation. The Cambridge dictionary defines manipulation as 'controlling someone or something to your own advantage often unfairly or dishonestly'. HIV positive asylum seekers and refugees could be manipulated to enrol in clinical trials in a number of ways. One of the participants attending the support group had been told by a researcher that the immigration authorities looked favourably on those who people who participated in trials. Luckily, she discussed this with her solicitor prior to enrolling and was informed that this was not the case. However, she was clear that had it been true, she would have enrolled

in the trial.

Other participants felt that they had not been given enough information by researchers prior to agreeing to participate and thus felt that they had been manipulated into participating due to their lack of knowledge. This was the case for two of the members of the support group who had enrolled in the clinical trial for the antiretroviral Fusion (T20), which needs to be injected at regular intervals to be effective. The participants stated that the researcher had omitted to mention that the preparation of these medications was very time consuming. Participants found themselves having to plan their normal activities around their next dose. When challenged by other members of the support group, they said that the PIS had specified the preparation time, but had not bothered to read this information feeling certain that the researcher would have informed them of any important aspects of the trial. It is possible that the researcher had genuinely not considered that preparation time would influence the decision to participate, but the members of the support group felt it more likely that he did not want to lose prospective participants as it was a difficult trial to recruit to.

Prospective participants can also be manipulated to participate if they are led to believe that they will benefit from the trial. While researchers may have reasonable grounds to suspect that the trial medication could be effective, they are not in a position to give a categorical assurance to research participants that this will be the case. Some of the support group stated that they had agreed to enter a clinical trial

because their doctor seemed to be really enthusiastic about the new drug.

While these methods may be employed by researchers, the most common method of encouraging participation is by employing rational persuasion. Rational persuasion involves presenting a case based on facts that the individual already knows to persuade them to act in a certain way. For example, rational persuasion may be used to persuade a cyclist to wear high visibility clothing at night to reduce the risk of being hit by a car. The cyclist will know that he is more likely to be seen if he is wearing a fluorescent vest. He will also be aware that cyclists have a greater risk of being involved in road traffic collisions than other road users. Despite not being keen on wearing high visibility clothing, it is difficult for him to argue that this is not a sensible course of action to take. The researcher could employ this method to recruit to an HIV clinical trial. For example, the prospective participant is developing a drug resistance. Despite taking treatment as prescribed, his CD4 count is falling and he has a high viral load. He is aware that he will need to change to another class of antiretrovirals which will be more efficacious, and that his choice is limited due to the drug resistance. The researcher informs him that he is recruiting to a new drug trial on a new class of antiretroviral which could be effective in those with his type of drug resistance. If the researcher is aware that the prospective participant understands the need to change treatment and that the new trial drug has the potential to work, he could employ rational persuasion as a means of encouraging participation.

I will now look at inducements in clinical trials. Under clinical trials regulations researchers are permitted to offer inducements to trial participants, though these inducements must not be so large as to influence participation in clinical trials. These often take the form of vouchers or merchandise with the study label, such as sunglasses for those participating in studies relating to sun screening products. Researchers are also expected to recompense participants for any out of pocket expenses, such as travel and sustenance. The Nuffield Council on Bioethics (2002) does not have a problem with inducements unless they are excessive or if people are desperate, such as those who are in need of health care in developing countries. The Belmont Report (1979) defines undue inducements as 'an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance' and goes on to state that inducements in clinical trials can be problematic if the offer is large enough to override the individual's better judgement. The CIOMS guidelines state that 'if inducements are to be offered that should not be so large, however, or the medical services so extensive as to induce prospective participants to consent to participate in research against their better judgement'.

Researchers need to carefully consider inducements if they plan to recruit HIV positive asylum seekers and refugees to clinical trials. UK nationals who agree to participate in clinical trials may do so for a variety of reasons. They may have an altruistic desire to help others; they may be generally interested in research and want to have the opportunity to experience participation in a clinical trial. Others may be motivated to contribute to research for personal reasons, such as the development of

a disease in a loved one. Apart from participants in Phase One trials, which I do not intend to discuss here, very few will agree to enrol in a clinical trial for financial reasons, as the inducements are deliberately so small so as to not be a motivation for participation. Lott (2005) suggests rewards which the general population would not consider an incentive may be viewed as such by those who have very little. I agree that this may be the case for HIV positive asylum seekers who have no access to funds. For example, trial participants who are UK nationals would tend to view a thirty pound voucher per study visit as surplus pocket money. For HIV positive asylum seekers and refugees this may be the only funds they have access to and will use the voucher for basic essentials, such as food. This small inducement may be enough incentive to encourage participation.

Non-financial rewards for participation, such as medical treatment and care, may also be viewed as an inducement. Most UK nationals who are eligible for NHS treatment do not have any concerns about being charged for medical care even if out of work, as the NHS provides free treatment to all who are eligible. This is not the case for HIV positive asylum seekers and refugees. As discussed earlier, while they may theoretically have access to antiretroviral therapy, it is still subject to the interpretation of the NHS regulations by individual trusts. Some who are eligible may be charged and told that they can no longer access treatment until they pay. Some choose to access treatment via a clinical trial to ensure that they have continued access to treatment without the need to endure the legal quagmire. While they are a participant in a clinical trial they will also see medical staff during their routine study visits, where

they will be able to discuss any new health issues. The researcher can arrange clinical investigations to establish if the condition is related to the study medication. If it is related, it will be treated as a study related condition. Unrelated conditions would not be eligible for treatment either under the clinical trial or under the NHS. Is it ethical for researchers to investigate conditions which cannot be treated? It could be argued that if the prospective participant is informed during the consent process that new or unrelated conditions will not be treated under the clinical trial, and they agree to participate with that knowledge, the researcher has no obligation to treat. It could also be argued that the researcher will not know if the condition is trial related unless he conducts investigations, therefore the investigations are an intrinsic part of the study. However, if the investigations prove not to be study related, is it ethical for the researcher to withdraw the individual from the study without treatment, even if the individual has agreed this on the consent form? The Principal Investigator in HIV clinical trials is a doctor. Each doctor has a duty of care to his patients, whether in a clinical setting or research setting. I would argue that when the participant is enrolled in the clinical trial, the researcher assumes a duty of care towards that individual, including treating for any conditions which arise while the participant is under the care of the researcher. It would be unethical for the researcher to discharge having established that he has a condition which needs treatment without arranging for that treatment to be made available. If the participant is not eligible for NHS treatment and care, the researcher should arrange for the treatment to be available through the trial budget.

Harris (2010) states that the current guidelines - such as the CIOMS outlined above - are generally unsympathetic to the use of inducements in clinical trials. He also suggests that the CIOMS rationale for these guidelines such as 'someone without access to medical care may or may not be unduly influenced to participate, in research to receive such care' are confused.

He goes on to explore the factors which make an inducement undue. He does not believe that the level of the inducement undermines better judgement, or that the inducement influences the individual's decision to participate. He suggests that if this premise were true then

'all jobs with attractive remuneration packages would constitute 'undue' interference with the liberties of subjects and anyone who uses their better judgement to decide whether a total remuneration package plus job was attractive would have been unduly influenced'.

Harris differentiates between inducements which are undue, and undue inducements. The former refers to the nature of the inducement, not to the fact that it is being offered. The latter is the improper offering of inducements, improper because no inducements should be offered. He suggests that the guidelines refer to undue inducements, which are 'wrongly understood and wrongly applied'. I do not agree with Harris' premise that the level of inducement undermines better judgement, or that the inducement influences the individual's decision to participate. Many people would be

tempted to enrol in a clinical trial despite the risks if they were offered a large sum of money. This amount would vary depending on the personal situation of those asked. Certainly HIV positive asylum seekers and refugees who have no access to funds could be easily induced to participate against their better judgment. However, Harris' definition of an undue incentive could certainly be applied in this situation. It would be improper to offer inducements in this situation.

HIV positive asylum seekers and refugees may regard on-going health care as an inducement to participate in a clinical trial. The challenge researcher's face in HIV trials is how to avoid inducements if participation in itself is the inducement. For many HIV positive asylum seekers and refugees, the inducement to participate is access to medical staff and antiretroviral medication. Researchers cannot remove this inducement, for they are integral to the conduct of the study. In order to address this issue, I want to return to the Belmont Report's definition of inducement 'an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance'. I would agree that the provision of antiretrovirals may be viewed as an inducement, but I do not believe that the inducement is undue. As such, I believe that there is no intrinsic problem with permitting HIV positive asylum seekers and refugees to enrol in HIV clinical trials. While it would be correct to assume that some participants enrol in the clinical trial as a means of accessing treatment, others do not. We cannot assume that all HIV positive asylum seekers and refugees enrol in clinical trial for the sole purpose of accessing treatment and care. Indeed, some may have the same motivation as other individuals, such as a desire to further clinical knowledge and help future patients. While researchers may be aware that some

participant's motivation for enrolling in the trial is to access treatment, they are not setting out with the sole intention of recruiting from this population. The provision of antiretrovirals is an intrinsic part of the clinical trial. Providing them to participants cannot be considered 'excessive, unwarranted, inappropriate or improper' as inducement. However, the individual's lack of recourse to medication by any other means may certainly induce them to participate. While the researcher may not be offering treatment as an inducement, would the individual agree to participate in the trial if they could access treatment by any other means? Researchers could try to address this by assessing those potential participants who are HIV positive refugees and asylum seekers with a view to excluding those to whom access to an antiretrovirals may be an inducement. However, it is difficult to see how this could be achieved given that not all HIV positive asylum seekers and refugees enrol for the sole reason of accessing treatment and care and those who do are unlikely to state this is their reason for doing so. If we agree with Harris, it is the nature of the inducement which makes it undue. If antiretrovirals are an integral part of the clinical trial, it is difficult to see how they could be considered as an undue inducement in a clinical trial.

Psychological impairment

HIV positive asylum seekers and refugees may also be vulnerable in the research setting due to the physical and psychological effects of both HIV and their refugee status. I do not intend to discuss vulnerability due to lack of access to antiretrovirals

as this has been covered in previous chapters. Instead I will look at some of the psychological aspects of HIV which can increase vulnerability in HIV positive asylum seekers and refugees in the research setting.

Kalichman (2010) reported that stress - coupled with poverty and lack of access to adequate diet - influenced the ability of HIV positive individuals to adhere to treatment. This is certainly a situation which I have seen reflected in clinical practice in London. HIV positive asylum seekers and refugees often report that they are unable to take their antiretrovirals as prescribed. They may be housed with strangers in a hostel situation and be unable to store their medication as required for fear of others finding them and thus being alerted to their HIV status. Others report that they have had no money to purchase food and so have had to take their antiretrovirals on an empty stomach, which for some reduces absorption. Those who have failed their asylum appeals in the UK are not permitted to work - neither do they have access to social care. The National AIDS Trust (2010) reported that many of these individuals are dependent on voluntary organisations for the basic essentials. While this group may have access to antiretrovirals, the effects of poverty and lack of food increases their risk of developing drug resistant strains of the virus.

Antelman (2007) also reported high levels of anxiety, depression and posttraumatic stress disorder in asylum seekers. Many bear the scars of interrogations and torture, while a large number of both women and men reported being raped. Some have seen family members and loved ones killed and have suffered unimaginable terror fleeing

from oppressive regimes. These issues can have devastating and long term effects on the individual. They can also influence how they deal with others they perceive to be in a position of authority, such as medical staff. For example, during a routine hospital visit, the researcher may ask if they would be interested in participating in a clinical trial. They will be informed that participation is voluntary and that they are under no obligation to enrol. They will also be informed that their treatment at the clinic will not change should they decline to participate. However, their previous experiences make it difficult to believe that they will not face sanctions if they defy authority, in this case the researcher. In order to protect themselves from any retribution, they agree to participate.

Leaning (2001) suggests that refugees' lack of legal rights increases vulnerability. This is certainly true of those HIV positive asylum seekers and refugees who access clinical trials as a means of having continued access to treatment and care. They may not have chosen to participate if they had other options. They are also at risk of dispersal and deportation, which could affect their ability to continue to take antiretrovirals, potentially leading to the development of drug resistant strains of the virus.

While antiretrovirals have an important role in maintaining health, their ability to cross the blood-brain barrier may be limited. Heaton (2011) reported that HIV related neurocognitive impairment remains prevalent in this population, despite access to antiretrovirals. The effects of this impairment are subtle and may be missed by those

who have limited clinical experience. Valcour (2011) found that when questioned, patients seldom reported having any noticeable neurocognitive problems. However, on testing they had marked neurocognitive delay. If this condition is as prevalent as described, will it influence the individual's ability to consent for participation in clinical trials? The CHARTER study, described by Valcour, began recruitment in 1997 in the USA. It recruited 1600 HIV positive individuals' at all clinical stages and on a range of antiretrovirals. Half the participants were male, and half were either black American or African American. The number of refugees and asylum seekers was not reported. All the recruits underwent neurological testing under controlled conditions. The study is being extended to establish what - if any - effects these results have on the day to day functioning of HIV positive individuals. For the moment, it is unclear if these results will affect the individual's ability to understand and consent to clinical trials. However, the CHARTER study also reported high levels of suicide and suicidal ideation in the study population. The study did not record the immigration status of individuals so it is not possible to establish if the suicide risk was increased in this sub-population.

It would appear that HIV positive individuals are vulnerable to some extent due to the psychological effects of HIV. This psychological vulnerability is increased in those who are also asylum seekers and refugees.

Should vulnerable populations be permitted to enrol in clinical trials?

I have outlined some of the ways in which HIV positive asylum seekers and refugees

are vulnerable in the research setting. Some might argue that if this population is so vulnerable in the research setting they should not be permitted to participate in clinical trials. I disagree with this statement. Despite their vulnerability, I believe that this group should not be excluded from research. I will now go on to give reasons supporting this.

Is it necessary to recruit HIV positive asylum seekers and refugees to HIV clinical trials? Given their vulnerability, why recruit from this population at all? Some might consider that it would be more ethical to conduct HIV research on less vulnerable populations. Leaning (2001) suggests that the risk to refugees and asylum seekers from participating in research should not stop research from going ahead. Some research questions can only be answered by research within that population. I agree with Leaning and believe that the inclusion of HIV positive asylum seekers and refugees is essential to the development of new antiretrovirals. Antiretrovirals trials need to recruit HIV positive individuals to participate; it would be impossible to establish the safety, efficacy and resistance profile of new drugs without including this population. HIV positive individuals who are antiretroviral naïve are particularly valuable in the development of new drugs. UK nationals are more likely to be treatment experienced. Even those newly diagnosed may have acquired drug resistance, which excludes them from some clinical trials. However, asylum seekers and refugees are more likely to be antiretroviral naïve, which increases their value to researchers. In order to demonstrate the efficacy of new treatments, clinical trials need to have enough power to show a statistical significant. Given the number of HIV

clinical trials being conducted in the UK, I believe that it would be difficult to recruit fully to trials without the inclusion of HIV positive asylum seekers and refugees. Leaning goes on to remark that while the inclusion of refugees and asylum seekers is needed, there is little guidance on conducting research in refugee populations for researchers. She also believes that refugees and asylum seekers should be classed as vulnerable as this would afford them some protection in the research setting.

Lott (2005) suggests that vulnerable populations are attractive to researchers because of their vulnerability. This may be true to some extent in HIV positive populations. For example, an inexperienced researcher may be under pressure to recruit to an HIV clinical trial. He has a large cohort of patients, the majority of whom are eligible for NHS treatment and care; he has tried to recruit from this population with limited success. However, some of his patients are refugees and asylum seekers who are appealing to remain in the country on compassionate grounds, and require him to complete medical reports to support that application. While both groups are HIV positive, those entitled to NHS treatment and care will not be dependent on the researcher to provide letters of support for immigration authorities. The researcher cannot exploit that vulnerability to compel them to participate in a clinical trial.

One way to stop vulnerable individuals from being exploited would be to exclude them from research. This method was employed by The South African Clinical Trials Regulatory Authority. It had become concerned that vulnerable populations were being coerced into trials, indeed between 1997 and 1998, the number of clinical trials

increased by forty percent. These participants tended to have low levels of literacy and come from impoverished backgrounds. They were paid for their participation and some were also offered food vouchers. In order to combat what The South African Clinical Trials Regulatory Authority viewed as exploitation, it declared that all Phase One HIV trials participants should have completed twelve years of formal education. This was intended to protect participants by ensuring that they were able to understand the aims of the trials and give informed consent. However, as less than twenty percent of the population achieved this level of education, many of those who would have wished to participate were not able to do so. The response of the authorities certainly reduced the number of individuals who could be recruited to clinical trials, potentially limiting exploitation of vulnerable. I have a problem with this response for a number of reasons. While the increase in numbers recruited was undeniable, there was no evidence that this was due to coercion. If this were the case it would signify that the vast majority of researchers were acting in an unethical manner, which I feel to be unlikely. The South African Clinical Trials Regulatory Authority also justified this response on the inability of participants to understand consent forms. The low literacy levels of those participating in research reflect the levels seen in the general population. A more sensible approach would have been to require information to be imparted in a way which addressed the literacy levels. These individuals did not lack intelligence and capacity; they had not had the benefit of secondary education. Restricting access to the better educated skews any data collected as it is not representative of the population. The final point I take issue with is that it is the implication that it is wrong for individual benefit from participation.

While researchers can't offer participants' assurances that they will benefit from the trial medication, there are other advantages of participation. Steiner (2006) suggests that these include improved personal health, the positive feeling that comes from giving to others and being treated as partners in the research. For this vulnerable population the health benefits may include access to medical care, as well as access to food vouchers which will combat malnutrition and thus provide health gains. These participants were also being paid each time they attended a study visit. The authorities felt that this was an inducement, which could influence the individual's participation. The researchers argued that the amount of money was not large enough to be considered an inducement and that it was necessary to offer payment to ensure that participants returned for follow-up visits. The researchers concern that participants would not return unless they were paid would suggest that payment did influence participation. Why do we consider it wrong to pay participants when we think that it is OK to get paid for our time and effort in other situations? Many of us go to work each day. We have agreed our role with our employer, go to work each day, fulfil our duties and get paid for our efforts. This is no different from research participants. They agree to participate, attend study visits and get paid. These individuals are giving their time to the researcher. They will be undergoing clinical tests which may be painful and may be taking trial medication which could have side effects. Is it wrong to reward them for their efforts? Of course not. However, it would be wrong for the researcher to exploit their need for money to get them to participate in the clinical trial in the first place.

Harris (2010) states that we have a moral obligation to participate in scientific research, which can prevent serious harm and provide significant benefits. Participating in clinical trials benefits society by finding cures for diseases. He states that we have a moral obligation to help others ergo we should participate in clinical trials. He does go on to say that research should be underpinned by the obligation of the researcher to do no harm. As such, he must weigh up the harms and benefits and be able to justify the rationale for the research. I agree with Harris that we have a moral obligation to help others, and that this could be fulfilled by participating in a clinical trials. However, I might have compelling reasons why I can't participate and wish to help others in other ways. Indeed, there are not enough clinical trials worldwide to allow us all to participate, even if we had the desire to do so. If we agree that we have a moral obligation to participate in clinical research, it would be wrong to deny HIV positive asylum seekers and refugees the right to participate in clinical trials. However, they too can opt out of participation if they so choose. Harris goes on to suggest we have an obligation under justice to contribute to research. We all benefit from the fruits of research therefore we reciprocate. While I agree with this in general terms, it can be problematic in HIV research where the HIV population is small. The number of HIV trials is increasing year after year; there are observational trials, drug trials, and neurological based trials. The notice boards in clinics are papered with information about forthcoming trials and how important these are. If it were not for the requirement to have a break between trials, individuals could move from trial to trial year on year. Researchers stress the importance of these trials and are often unaware that the individual has trial fatigue and just needs some time to be a person,

not a clinical trial statistic.

HIV positive asylum seekers and refugees are particularly vulnerable due to their lack of access to health care. While they may legally be entitled to antiretrovirals while waiting to be deported, they may find it difficult to overcome obstacles to access these drugs. In addition, while they can access emergency services, they are not entitled to NHS treatment and care and may be charged if they become unwell. In order to have regular access to antiretrovirals and medical treatment, some HIV positive asylum seekers and refugees enrol in clinical trials. They may not have chosen to enrol in a clinical trial if they had any other means of accessing care; without continued access to treatment and care they are at risk of developing opportunistic infections and eventually death. Some argue that HIV positive asylum seekers and refugees vulnerability - due to their need access treatment and care - precludes them for participation in clinical trial. I would suggest that those who enrol in trials as a means to access treatment do so after having carefully weighed up their choices, and choosing the option which has the best outcome for them. Some might argue that this need to access care invalidates consent. Wilkinson (2003, p.80) presents an alternative to this. He states that it would be quite bizarre to rule out the possibility of valid consent if the individual has no acceptable alternatives. He gives two reasons for reaching this conclusion. He begins by saying that it is difficult to specify non-arbitrarily what counts as a sufficient number of good alternatives. HIV positive asylum seekers and refugees have limited options. None of these options are ideal, but some may be some more attractive than others. Secondly, he thinks it

strange that if one had an entirely free choice between option X, which is extremely good, and option Y, which is extremely bad, than that the person could not validly consent to X because of lack of acceptable alternatives. Let us apply this to our HIV positive asylum seeker. Option X would be accessing health care and option Y would be death. It would be bizarre if the individual chose death when the other option is so much more attractive.

I believe that there are compelling reasons to permit HIV positive asylum seekers and refugees to enrol in clinical trials, despite their increased vulnerability in the research setting. They have the same moral obligations to participate in research as the rest of society, and should not be denied the opportunity to contribute if their decision to do so is given freely. Some may enrol as a means of accessing health care, which for them would be a benefit of participation. Provided that the risks of participating do not outweigh their health care needs they should be allowed to participate. Singh (2006) suggests that over protectionism can lead to unethical outcomes. I believe that over protectionism in the form of denying HIV positive asylum seekers and refugees access to clinical trial can result in lack of medical treatment and care leading to ill health and death. This would be unethical and detrimental to this population.

The role of the ethics committee in protecting vulnerable populations.

As part of their role, RECs ensure that researchers take the appropriate measures to protect vulnerable populations from harm. Neither the Declaration of Helsinki nor the Council for International Organisations of Medical Sciences (CIOMS) specifically

mentions refugees when discussing vulnerable participants. In the UK, HIV positive asylum seekers and refugees are not recognised as a vulnerable population by NRES. It is left to the discretion of the individual researcher to indicate on the ethics application form if they consider this group to be vulnerable, and then outline what measures they plan to take to address any ethical issues of recruiting them to a clinical trial. I am a member of a research committee which reviews HIV clinical trials on a regular basis. While I recognise that researchers are not required to recognise refugees and asylum seekers as a vulnerable population, I find it quite concerning that many of these doctors fail to highlight any ethical considerations. Indeed, a few have argued that those living with HIV are no more vulnerable in the research setting than any other population. All work within the HIV setting and care for patients who are asylum seekers and refugees. They will have attended multidisciplinary meetings where other team members such as social workers and psychologists discuss issues which have a bearing on the patient's well-being. In their clinical role they are responsible for writing supporting letters for asylum appeals. It is inconceivable that these doctors will be unaware of the vulnerability of this group of patients in a clinical setting. However, they seem unable to relate this to clinical research. Provided that there are no other ethical issues, the REC seldom challenges the assertion of the researcher and grants approval for the study.

Nicholson (2002) too does not preclude vulnerable individuals participating in a clinical trial. However, he does stipulate that the level of vulnerability should be reduced as far as possible by researchers and research ethics committees. He

suggests that this can be achieved by ensuring that the individual has understood the research, is free from duress and able to give voluntary informed consent. While I agree with Nicolson that RECs need to do more to protect the vulnerable, I believe that they need to do much more than just checking understanding and ensuring that participants are free from duress.

I do not believe that RECs go far enough to protect the interests of HIV positive asylum seekers and refugees in the research setting. This may be due to the lack of knowledge about the needs of HIV positive asylum seekers and refugees. It may also be due to the desire not to slow down research which was discussed earlier in this chapter. Some might argue that the failure of NRES to consider HIV positive asylum seekers as a vulnerable population constrains RECs to what measures that researchers can take to address any vulnerability in clinical trials. While identifying this population as vulnerable would undoubtedly afford them more protection, RECs can take measures under the existing guidelines which will afford an increased level of protection to this population. If HIV researchers have not highlighted any ethical considerations in their application, the REC can ask if they expect HIV positive refugees and asylum seekers to be included in the study population. If they confirm that this population will be included, they should be asked to outline any ethical concerns and what measures they intend to take to address these issues. Researchers who say that they do not intend to recruit from this group should be asked if they have considered the demographics of the proposed research population. Unless the researcher specifies a group that is unlikely to include HIV

positive asylum seekers and refugees, The REC should - as above - ask him to outline any possible ethical considerations and measures he would take to address these. I believe that the REC is justified in asking for these measures. Their role is to protect the well-being and safety of trial participants. Unless these measures are taken, HIV positive asylum seekers and refugees will continue to be vulnerable in the research setting.

Summary

In this chapter I have outlined some of the reasons why I think HIV positive asylum seekers and refugees should be considered as a vulnerable population in research. These are multifactorial; this group suffers from chronic ill health from a condition which requires lifelong treatment to keep it under control. While HIV positive asylum seekers and refugees are legally entitled to antiretrovirals until they are returned to their country of origin, they may find barriers to treatment due to local bureaucratic practices. In addition, while they can access emergency treatment for other conditions, on-going treatment is still chargeable. While antiretrovirals can stop viral replication, they too have side effects. As such, those who have the virus are at increased risk of developing depression and other psychological conditions. Depression too is more common amongst asylum seekers and refugees, with HIV positive asylum seekers and refugees at the greatest risk from psychological distress. Their refugee status also engenders them more vulnerable. They may find it difficult to decline participation in a clinical trial if they are asked to do so by someone they perceive to be in a position of authority, such as a doctor. They are often reliant on

medical staff to provide letters of support for asylum claims. The individual's cultural background can also make it difficult to refuse a request which comes from someone with a perceived higher social status, such as a doctor.

Despite their vulnerability, there are measures which can be taken which will afford HIV positive asylum seekers and refugees additional protection in the research setting. Firstly, NRES should recognise that asylum seekers and refugees are a vulnerable population in research and add them to the list of those considered vulnerable on the IRAS application form. The REC should ask researchers who are conducting HIV clinical trials if they plan to recruit from this population and if so what measures they have in place to protect them. Those who lack capacity should not be excluded from research but an independent legal representative should be appointed to consent on their behalf if the family are unaware of the individuals HIV status. While I consider HIV positive asylum seekers and refugees to be vulnerable in the research setting, I do not believe that this should stop them from participating in research. I believe that employing the measures outlined above will reduce the risk of harm, thus enabling them to participate in clinical trials if they so wish.

Chapter 8- Conclusion

While HIV cannot be cured, it can now be kept under control with antiretroviral medications. In countries such as Britain, where there is access to treatment, HIV is now considered to be a long-term medical condition similar to diabetes. Public awareness of HIV has also improved. While some stigma remains, campaigns by both the government and HIV charities have done much to dispel myths around transmission. In contrast, the outlook is poor for those who either live in areas where they have no access or are unable to afford treatment. Until 2012, HIV positive asylum seekers and refugees in Britain who had their asylum claims refused were not eligible for treatment. In order to continue treatment, some enrolled in clinical trials. While the majority of asylum seekers and refugees now have access to treatment and care, there still remains confusion around the eligibility criteria. THT (2012) reports that HIV positive individuals are being denied treatment that they are legally entitled to receive, or being charged for treatment which should be free to them. As such, some individuals may be afraid to access treatment which they are eligible for. Some are also concerned that the eligibility criterion will change yet again, leading to further withdrawal of treatment. This assertion may be justified to some extent in light of David Cameron's recent speech (2013) where he outlined the government's plans to 'toughen up' on asylum seekers and refugees. As such, some asylum seekers and refugees choose to access clinical trials as a means of accessing treatment.

In this thesis I have looked at some of the ethical issues surrounding the recruitment of HIV positive asylum seekers and refugees to HIV related clinical trials in Britain.

While all participants in clinical trials are vulnerable to some extent, I have shown that HIV positive asylum seekers and refugees are at a increased risk. Despite this, HIV positive asylum seekers and refugees are not given specific consideration in the research setting. In this final chapter I will reiterate what I believe to be the main areas for concern and outline what measures should be taken to address these issues.

Researchers applying for ethical approval for studies in the UK are required to do so using the IRAS system. Researchers are asked if they plan to recruit from vulnerable populations and are provided with a list of those considered to be vulnerable by NRES. If the intended target group is considered to be vulnerable, the researcher must outline what measures they intend to take to ensure that the participants are not further disadvantaged by participating in the trial. Their responses are assessed by the REC prior to issuing approval. HIV positive asylum seekers and refugees are not listed as a vulnerable population on the IRAS application form. It is left to the discretion of individual researchers if they want to identify them as such and outline what steps they plan to take to address their needs. We have seen that HIV positive asylum seekers and refugees are vulnerable in the research setting. They are vulnerable due to their immigration status; they may feel under pressure to enrol in trials as they need letters of support from their physician to submit to immigration authorities. They are vulnerable because they have HIV; without access to medical treatment their prognosis is very poor. Participation in a clinical trial may be one means of accessing treatment. They may be vulnerable due to their cultural

background; they may find it difficult to decline to participate in a clinical trial if asked to do so by someone they perceive to have a high social standing. They may be vulnerable due to lack English as a first language; they may not understand requirements of trial participation. Unless they are identified as a vulnerable population they will continue to be at increased risk in the research setting. In order to rectify this, NRES should recognise HIV positive asylum seekers and refugees as vulnerable. Once they are identified as a vulnerable population, researchers will then be required to identify the measures they intend to take to deal with issues, which should include all of the measures listed below.

We have seen that some HIV positive asylum seekers and refugees enrol in multiple clinical trials and may also over-participate by enrolling in back to back trials. This practice is not confined to HIV positive individuals enrolling in clinical trials but is seen in other study populations who are not HIV positive. This practice can be dangerous for the individual, who may be subjected to numerous clinical tests and drugs. It can also affect the integrity of the trial data. The TOPS scheme has proven to be very effective in reducing this practice in Phase One trials, where a register is kept of participants and available to other trial centres. Participants are required to give a unique form of identification, such as a passport or NI details shared with other trials. In order to rectify this, the TOPS scheme should be expanded to include Phase Two to Four clinical trials in order to reduce the risk of multiple and over-participation. This may be more challenging for trials involving asylum seekers and refugees as many will not have passports or NI numbers. However, all asylum seekers and refugees are

issued with documents from the immigration authorities and the current system could be adapted to accept these as a form of identification. As with the current scheme, consent to checking should be a prerequisite to enrolling in a clinical trial. All PIS should be required to expand the section asking if participants have recently or are currently participating in a clinical trial to outline the potential risks of over and multiple participation. Researchers may argue that the cost of funding such a scheme would be prohibitive, or that research would be slowed while checks were taking place. However, the current TOPS scheme has not found this to be a problem. Until the scheme has been expanded to cover all clinical trials, prospective participants will continue to enrol in multiple trials and over participate. Those who do so put themselves at risk and also affect the integrity of trial data.

Researchers are required to provide trial information to prospective participants, including the aims and objective of the trial, and risks and burdens. NRES provides comprehensive guidance as well as templates which are available to researchers. There are very specific issues which are relevant only to HIV positive asylum seekers and refugees. I would argue that this information is necessary for them to make an informed choice about participation and should be added to the list of templates available to researchers. This information should include the risk of developing drug resistant strains of the virus should they have to abruptly stop treatment through dispersal or deportation. Participants should be clearly informed that it is unlikely that participation in the trial will positively influence the outcome of any asylum application. Participants should be informed of the risks of over and multiple participation. The

current PIS informs participants that their treatment and care will not be affected should they decline to participate. I would suggest that this statement be strengthened for HIV positive asylum seekers and refugees. Participants should be informed that they are under no obligation to participate even if asked to do so by their clinician.

Despite following guidance, PIS are often not user friendly and may not be understood by the target population. NRES suggests that researchers liaise with patient groups when considering developing research protocols. I would suggest that one area where the expertise of local groups can have the greatest impact is in the development of PIS. Not only are the groups aware of language and cultural issues, they will be able to discuss the most appropriate ways to raise the topic with community groups. NRES should strengthen their position and move from suggesting that researchers involve patients groups to making it a mandatory requirement. Joint collaboration between researchers and community groups will ensure that the PIS not only contains the essential information about the trial, but that the information is presented in a culturally appropriate and easily understood format. The sheet should then be piloted with a group of participant representatives who were not involved in the development of the PIS. NRES guidance does not limit researchers from providing information only in written form. Some community groups have suggested that they would prefer information verbally in a group setting, or by other auditory forms such as tape or DVD. This format could be very useful if potential participants have low levels of literacy. It could also be utilized to provide information in the

participants own language in situations where it is difficult to find an interpreter, for example if the participants has a first language which is not common. However, researchers should also be required to translate the PIS when this is practical. At present, researchers often state that it is not cost effective to translate the PIS, despite the target population not having English as a first language. The REC has no means to compel them to do so. The cost of translation should be factored in the trial budget if the majority of prospective participants are identified as belonging to a population that does not have English as a first language, and are not likely to have a good understanding of English. Researchers should be expected to give a reasonable explanation to the REC if they are not planning to do so and offer alternative ways of imparting information.

Many HIV positive asylum seekers and refugees will not have English as a first language. While they may be able to understand basic spoken language they could have difficulty understanding the concepts of a clinical trial. Most researchers now have access to interpreters who are able to translate trial information. While these interpreters may be very skilled, they could have very little understanding of clinical trials and may find it difficult to impart this information to participants. The training for interpreters does not include translating in clinical trials. In order to rectify this NRES - in conjunction with governing bodies of interpreters - should set standards for interpreters working within clinical trial settings and develop an accredited training program.

Possibly the greatest risk to clinical trials participants who are HIV positive asylum seekers and refugees is the risk of being dispersed or deported resulting in the development of drug resistance. Individuals are seldom given any notice that they are being moved by authorities and may not have had time to collect antiretroviral medication. Others may not be permitted to take medication with them or have it removed by authorities for safe keeping. Patients themselves may be unaware that they will be at a increased risk of developing drug dependency if they have to stop their antiretroviral medication in an unstructured manner such as this. As outlined above the participant information sheet should clearly outline the risks of developing drug resistance. Researchers should consider providing all participants with a 'withdrawal pack' of antiretroviral medication. This would include details of how to safely stop treatment thereby reducing the likelihood of developing drug resistance. I would argue that the authorities responsible for the dispersal or detention of refugees and asylum seekers should ensure that they have policies and procedures in place to deal humanely with HIV positive individuals, and reduce the potential for exacerbating HIV related health problems while they are in custody. This is a concern not only for those participating in clinical trials, but for all HIV positive asylum seekers and refugees. As the authorities are responsible for the safety of detainees, it is reasonable for them to remove medication initially to check that it has been prescribed. However, there is often a long delay before this confirmation comes and an even longer delay before the treatment is recommenced. During this time, the individual may be at risk of developing drug resistance. Detainees have also voiced concerns about how staff treat HIV positive individuals, such as wearing gloves and a

mask while talking to them. In order to address these issues I would suggest that a working party be established comprising of the Immigration Authorities, detention centres and representatives of BHIVA and BASHH. This working party should establish guidelines to ensure seamless treatment for HIV positive detainees. It would be relatively easy for HIV physicians to give all HIV positive asylum seekers a three day supply of treatment and a letter confirming that the individual is on treatment. This could be given to the officials when the individual is detained, ensuring that the participant has enough medication until they are seen by a medical officer. There should be closer liaison with HIV physicians to ensure that medical problems are addressed in a timely manner to reduce the risk of complications. All staff working in detention centres should have mandatory training on HIV. In addition to explaining the importance of continued treatment, it will also allay some of the concerns staff have regarding transmission.

Research Ethics Committees are pivotal in ensuring that the specific needs of HIV positive asylum seekers and refugees are being considered. The role of the REC is to protect the interests of those participating in research while supporting the development of new medications or knowledge gained through knowledge. These two aspects can conflict when pressure is placed on the REC to approve clinical trials at their first presentation. Minor issues such as providing translations of the PIS may be overlooked if the trial has no other obvious ethical concerns. However, the REC has a responsibility to ensure that information provided to participants is in a format which is culturally and linguistically appropriate to them. As such, they should actively support

researchers who utilise alternative methods of providing trial information, such as the use of visual aids and group discussions. RECs should ask researchers who plan to conduct research with HIV positive participants what provision they have made for asylum seekers and refugees. Those who state that they do not plan to recruit from this population should be challenged; the likelihood that they will not recruit an asylum seeker or refugee is very small.

In conclusion, while the inclusion of HIV positive asylum seekers and refugees in clinical trials raises ethical concerns, they should be supported to participate in clinical trials if their decision to participate is based on information they can understand, that their decision to participate is given freely with no coercion and that they are aware of both the risks and benefits of participation. There has been very little published on the issues relating to the participation of HIV positive asylum seekers and refugees in clinical trials. In this thesis I have highlighted some of the issues which contribute to what is already known of this topic. If the recommendations I have made in this chapter are implemented, it would go some way to addressing the specific needs of this population should they choose to participate in clinical trials.

References

The Adults with Incapacity (Scotland) Act 2000 www.uk-legislation.hmso.gov

Accessed 3/3/2013

AIDS Clinical Trials Group (1996) 076 Trial- Analysis Emphasis's Importance of Offering AZT Therapy to all HIV-Infected Pregnant Women *HIV National Institutes of Health* www.nih.gov/news/pr/nov96 Accessed November 2008

AIDSmap (2007) A to Z of clinical tests www.aidsmap.com Accessed 12/7/08

Aidsmeds and poz (2008) Special issues for children with HIV <http://aidsmeds.com/articles/children> Accessed 12/11/08

African HIV Policy Network (2007) Encouraging Community HIV testing *African Policy Network*

Akkad a, Jackson C, Kenyon S, Dixon-woods M, Taub N, Habiba M (2006) Patients' perceptions of written consent: questionnaire study *British Medical Journal* 333:528

Ames J, Thurston, M., (2008) Trials and Treatments: some reflections on informed consent and the role of research ethics committees *Research Ethics Review* 4 (3): 95–100

Amnesty International (2006) Down and Out in London- The road to destitution for rejected asylum seekers *Amnesty International UK*

Annas GJ, Grodin MA, (1998) Human rights and maternal-fetal HIV transmission prevention trials in Africa *American Journal of Public Health* 88(4): 560-562

Antelman G, Kaaya S, Wei R (2007) Depressive symptoms increase risk of HIV disease progression and mortality among women in Tanzania *Journal of Acquired Immune Deficiency Syndrome* 44:470-477

Appelbaum P, Lidz, C., Kitzman, R. (2009) Voluntariness of Consent to research: A conceptual model *Hastings Centre Report* 39 (1):3

Appelbaum P, Lidz C, Kitzman R. (2009) Voluntariness of Consent to research: A preliminary Empirical Investigation *Hastings Centre Report* 30 (6): 10-14

Aspinall PJ, (2005) Why the census needs to ask about language *British Medical Journal* 331: 363-364.

Association of the British Pharmaceutical Industry (1988) *Payment for volunteers in*

Phase 1 clinical trials ABPI press London

Association of the British Pharmaceutical Industry (2007) *Guidelines for Phase 1 clinical trials* ABPI press London

A V Department of Health and West Middlesex University Hospital NHS Trust (2008)
Neutral Citation Number: (2008) EWHC 855 *Crown Copyright*

Avert (2006) The Impact of HIV & AIDS in Africa

<http://www.avert.org/aids-impact-africa.htm>

Accessed 18/12/09

Avert (2006) Universal Access to AIDS treatment: Targets and Challenges

<http://www.avert.org/universal-access.htm>

Accessed 28/11/11

Avert (2007) AIDS Orphans <http://www.avert.org/aidsorphans.htm>

Accessed 11/12/08

Avert (2009) HIV Types, subtypes groups and strains

<http://www.avert.org/hivtypes.htm>

Accessed 10/04/09

Avert (2011) AIDS Orphans <http://www.avert.aids-orphans>

Accessed 28/11/11

Batty D, (2009) Clinton backs violation of AIDS drug patents *Guardian*

Beauchamp T, Childress R, (2001) Principles of Biomedical Ethics 5thed Oxford University Press

The Belmont Report (1979): ethical principles and guidelines for the protection of human participants of research

National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research <http://ohsr.od.nih.gov/guidelines/belmont.html> Accessed November 2012

Bennett R, Draper H, Frith L (2000) Ignorance is bliss? HIV and moral duties and legal duties to forewarn *Journal of Medical Ethics* 26: 9 - 15

Bhopal R, (2008) Ethical issues in health research on ethical minority populations: focusing on inclusion and exclusion *Research Ethics Review* 4 (1): 15-19

Bluthenthal RN, Palar K, Mendel P, Kanouse DE, Corbin DE, Derose KP (2012)

Attitudes and beliefs related to HIV/AIDS: Barriers and opportunities for HIV related

intervention *Social Science Medicine* 74 (10): 1520-1527

Boyce M, (2003) The Over-volunteering Prevention System (TOPS) *British Journal of Clinical Pharmacology* 55: 418

Boyce M, Walther M, Nentwich H, Kirk J, Smith s, Warrington S (2012) TOPS: an internet-based system to prevent health subjects from over-volunteering for clinical trials *European Journal of Clinical Pharmacology* accessed via *Springerlink.com*

Braunholz DA, Edwards SJ, Lilford RJ (2001) Are randomized clinical trials good for us (in the short term)? Evidence for a 'trial effect' *Journal of Clinical Epidemiology* 54(3): 217-24

Breen LM, What should I do if my patient does not speak English? *Journal of American Medical Association* 282: 819

British Association for Sexual Health and HIV (2006) UK Guidelines for the use of post exposure prophylaxis following sexual exposure to HIV
<http://www.bashh.org.uk/guidelines>

British HIV Association (2001) The role of adherence in HIV disease *BHIVA publications*

British HIV Association (2008) UK National guidelines for HIV testing *BHIVA Press*

British HIV Association (2008) Guidelines for the treatment of HIV-infected adults with antiretroviral therapy *BHIVA Publications*

British HIV Association and the National AIDS Trust (2009) Detention, Removal and People Living with HIV: advice for health care and voluntary sector professional *BHIVA publications*

British Medical Association (2011) Access to health care for asylum seekers and refused asylum seekers *BMA publications*

Brody H, (1999) Transparency: Informed consent in primary care. In Arras, J. and Steinbock, B (eds): Ethical Issues in Modern Medicine (5th Ed). *Mountain View: Mayfield publishing Company*

Brown GJ, (2000) Recruiting Human Subjects-Pressure in Industry –Sponsored Clinical Research. *Department of Health and Human Services Office of Inspector General*

Burnett J, Fessahaye E, Stopes (2010) Grave Breaches; failure to provide NHS equivalent care to immigration detainees with HIV *Medical Justice Report*, London

Cameron D (25th March 2013) Immigration and welfare reform speech delivered to University Campus Suffolk www.gov.uk/government/speechers/davidcameron
Accessed 28th March 2013

Carter M, (Ed) (2007) Anti-HIV drugs *The National AIDS Manual eighth Edition* p.3

Chatora v, et al (2010) Drug resistance related to AIDS, Tuberculosis and Malaria in the African Region *The African Health Monitor* 11 January-March

Clutterbuck D, Flowers P, Fakoya A, Barber T, Wilson H, Nelson M, Kapp S, Hedge B, Sullivan AK (2011) UK National Guidelines on Safer Sex *The Clinical Effectiveness Group of the British Association for Sexual Health and HIV and the British HIV Association*

Cohen M, Febri M, Cai X, Shi Q, Hoover D, Binagwalo A, Culhare M, Mukanyonga H, Karegoya D, Anaston K (2009) Prevalence and Predictors of Posttraumatic Stress disorder and depression in HIV affected and at risk Rwandan women *Journal of Women's Health* 18 (11): 1783-1791

Collins S. (2012) Disastrous Warning for Global HIV programs in 2012 *HIV Treatment Bulletin* 13(1/1)

Connor C, et al (1994) Reduction of Maternal-infant Transmission of HIV 1 with Zidovudine Treatment: Paediatric AIDS Clinical Trials Group Protocol 076 Study Group *New England Journal of Medicine* 331: (18)

Coovadia HM, Rollins NC, Bland RM, Little K, Coutoudis A, Berrish ML, Newall ML, (2007) *Lancet* 369 (9567): 1107-16

Council for International Organisations of Medical Sciences and World Health Organisations (2002) International Ethical guidelines for Biomedical Research Involving Human Subjects, Guideline 13 *World Health Organisation, Geneva*

Cooper DA, (2008) Life and death in the cART era. *The Lancet* 372: 266 - 267

Crown Prosecution Service (2008) Guidance regarding reckless transmission of HIV www.cps.gov.uk Accessed July 2010

Creighton S, Sethi G, Edwards SG, Millar R, (2004) Dispersal of HIV positive asylum seekers: national survey of health care providers *British Medical Journal* 329 (7461): 322-323

Dawson A, (2009) 'The Normative Status of the Requirement to Gain an Informed Consent in Clinical Trials: Comprehension, Obligations and Empirical Evidence' in Corrigan O, Liddell K, McMillan J, Richards M, Weijer C, (eds) *The limits of Consent :*

A Socio-legal Approach to Human Subject Research in Medicine *Oxford University Press*

De Melo-Martin I, Ho A, (2008) Beyond Informed Consent: the therapeutic misconception and trust *Journal of Medical Ethics* 34: 202- 205

De Mendoza C, (2009) HIV viral load monitoring in Developing Countries *Future Virology* 4(5): 423-430

Department of Health (1991) Local Research Ethics Committees *HSG (91)5 London*

Department of Health (1997) Ethics Committee review of multi-centre research *HSG (97)23 London*

Department of Health (2008) Failed Asylum Seekers and Ordinary Residence-Advice to Overseas Visitors Managers *DOH gateway reference 9854*

Department of Health (2012) HIV treatment for Overseas Visitors <http://www.dh.gov.health/2012/09/hiv-overseas-visitors> Accessed November 2012

Education Program Development Fund (2007) *EFI FTI Secretariat*

Elbe, S (2005) AIDS, Security, Biopolitics *International Relations* 19 (4): 403-410

European Court of Human Rights (1/6/2010 as amended by protocols number 11 and 14) Convention for the Protection of Human Rights and Fundamental Freedoms

English V, Mussell R, Sheather J, Sommerville A, (2005) Expulsion of failed asylum seeker suffering from AIDS, *Journal of Medical Ethics* 31: 495-496

Erickson S, Helesson G, (2005) Keep People Informed or Leave Them Alone? A suggested Tool for Identifying Research Participants Who Rightly Want Only Limited Information *Journal of Medical Ethics* 31: 674-678

Erin CA, Harris J (2002) AIDS: ethics Justice and Social policy *Journal of applied Philosophy* 10: 165 – 173

European Union Clinical Trials Directive 2001/20/EC

Expert Advisory Group on AIDS (2004) HIV Post-Exposure Prophylaxis: Guidance from the UK Chief Medical Officers' Expert Advisory Group *Department of Health*

Faculty of Sexual and Reproductive Health Care (2007) Clinical Guidance- male and female condoms *Royal College of Obstetrics and Gynaecology*

Federal Drug Agency (2011) Drugs for Human Use *Code of Federal Regulations*,

Feroze U, Martin D, Kalantar-Zadeh K, Kim JC, Reina-Patton Kopple JD (2012)
Anxiety and Depression in Maintenance Dialysis Patients: Preliminary Data of Cross-sectional Studies and Literature Review *Journal of Renal Nutrition* 22 (1): 207-10

Field S, (2010) Leading the Way: High Quality Care for all through General Practice
Royal College of General Practitioners

Gallo RC, (1986) The first Human Retro Virus *Scientific American* 255: 78-88

Garrard E, Dawson A, (2005) What is the role of the research ethics committee?
Paternalism, inducements, and harm in research ethics *Journal of Medical Ethics* 31:
419-423

Gazzard B, Anderson J, Ainsworth J, Wood C, (2005) Treat with Respect: HIV, Public
Health and Immigration, London Expert Panel report to the All Party Parliamentary
Group on AIDS

General Medical Council (2006) Good Medical Practice *GMC publications*

General Medical Council (2009) Tomorrows Doctors *GMC publications*

Gillon R, (2001) Fully informed consent, clinical trials and the boundaries of therapeutic discretion. In *Informed Consent in Medical Research* Doyle, L. and Tobias, J.S. (eds) *BMJ Books* p. 263-264

Glantz LH, et al (1998) Research in Developing Countries; Taking Benefit Seriously *Hastings Centre Report* 28: 38-42

GlaxoSmithKline (2011) Frequently asked questions about pharmaceutical research
<https://us.gsk.com/html/healthcare-common-questions.html>

Goggins M, (2005) Introduction to the work of research ethics committees in the United Kingdom: what is involved on being on a research ethics committee. 3rd edition *Association of the British Pharmaceutical Industry*.

Governance Arrangements for Research Ethics Committees (2001) *Department of Health*

Gunn V, Bryant D, Sommerville L, Birmingham T, Oxman A (2009) Outcomes of Patients who participate in RCTs compared to similar patients receiving similar interventions who do not participate *Cochrane Review* Issue 2

Hamill M, McDonald L, Brook G, Murphy S (2004) Ethical and legal issues in caring for asylum seekers and refugees in the UK *Bulletin of Medical Ethics* 203:17-21

Harris J, (2010) The Ethical Case for Making Better People *Princeton University Press*, p 202- 208

Harrigana R, Whaley M, Montaner J (1999) Rate of HIV-1 RNA rebound upon stopping antiretroviral Therapy *AIDS* 13 (8): 59-62

Health Protection Agency (2006) A complex Picture HIV and other Sexually Transmitted Infections in the United Kingdom: 2006 *HIV/STI Division, Communicable Disease Surveillance Centre and the Scottish Centre for Infection and Environmental Health*.

Health Protection Agency, (2007) HIV and STI's specific to Black African and Black Caribbean Data *HIV/STI Division, Communicable Disease Surveillance Centre and the Scottish Centre for Infection and Environmental Health*.

Health Protection Agency, (2010) HIV in the UK: 2010 report *HIV/STI Division, Communicable Disease Surveillance Centre and the Scottish Centre for Infection and Environmental Health*.

Heaton RK, Clifford DB, Franklin DR (2011) HIV associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study *Neurology* 75: 2087-2096

Heckler H, (2009) Effects of the Global Economic Crisis: Examining the Impact of HIV and AIDS Funding

<https://www.ngopulse.org/article/effects-global-economic-crisis-examining-impact-hiv>

Helgesson G, Ludvigson J, Gustafsson Stolt U, (2004) How to Handle Informed Consent in Longitudinal Studies when Participants have a limited Understanding of the Study *Journal of Medical Ethics* 31: 670-673

Hill Z, Tawiah-Agyemang C, Odei-Danso S, Kirkwood B (2008) Informed Consent in Ghana: What do Participants Really Understand *Journal of Medical Ethics* 34: 48-53

Home Office UK Border Agency Dispersal Order

Hornbeck R, (2005) Price discrimination and smuggling of HIV drugs *Topics in Economic Analysis and Policy* 5: 16

Human D, (2001) When are Placebo controlled Trials Ethically Acceptable *WMA publications*

Hutchinson C (1998) Phase 1 Trials in Cancer Patients: Participants Perceptive *European Journal of Cancer Care* 7(1): 15-22

i-Base (2012) Introduction to combination therapy *i-Base publications*

Inegbenebor D, KumbaSagbe F, Stevenson J, Sinyemu E, Kamaru M (2012) 'I'd rather be in prison' – Experiences of Africans in Immigration and Removal Centres in the UK *African Health Policy Network*

Integrated Research Application System (2008) Legal and ethical requirements for informed consent *NRES*

International Conference on Harmonisation of Technical requirements for Registration of Pharmaceuticals for Human Use (2000) Topic M3 (R1) Non-clinical safety studies for the Conduct of Human Clinical Trials for Pharmaceuticals p3, 1.4 *European Medicines Agency*

The International Code of Marketing of Breast Milk Substitutes (updated 2008) Frequently asked questions *WHO library*

International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice (1996) *The Institute of Clinical Research* 9 ICH 1996, s.4.8.10

Joffe S, Cook E.F, Cleary PD, Clark JW, Weeks JC (2001) Quality of informed consent in cancer clinical trials; a cross-sectional survey *Lancet* 358: 1772-1777

Kale R, Kunj L, (1997) Failing to seek patient consent to research is always wrong
British Medical Journal 314: 1081- 1082

Kalichman SC, Grebler T (2010) Stress and poverty predictors of treatment adherence among people with low literacy living with HIV/AIDS *Psychosomatic Medicine* 72: 810-816

Katz J, (1984) *The Silent World of Doctor and Patient*. New York Free Press

Katz J (1996) Human sacrifice and Human Experimentations: Reflections on Nuremberg *Occasional Papers, paper 5, Yale Law School Legal Scholarship Repository*

http://digitalcommons.law.yale.edu/ylspo_papers/5 Accessed 11/11/11

Kilbom U, (2007) Autonomy and Negatively Informed Consent *Journal of Medical Ethics* 32: 146-149

Kiplis K, Vulnerability in Research Subjects *Newsletter on Philosophy and Medicine APA* 14 (1): 9-11

Kottow M, (2002) the Vulnerable and the Susceptible *Theoretical Medicine* 23: 461-471

Lantos J (1999) The Inclusion Benefit in Clinical Trials *Journal of Pediatrics* 134: 130-131

Leaning J, (2001) Ethics of research in Refugee Populations *Lancet* 357: 1432-1433

Leight S, (2003) The application of vulnerable populations' conceptual model to rural Health *Public Health Nursing* 20 (6):440-48

Levine C, et al (2004) The limitations of Vulnerability as a Protection for Human Research Participants *The American Journal of Bioethics* 4(3): 44-49

Liberty (2008) Evidence to the Joint Committee on Human Rights: Treatment of Asylum seekers *Liberty Publications*

Lim M, (2002) Questioning the Voluntary Nature of Informed Consent *Virtual Mentor* 4 (10)

Lott J, (2005) Module Three: Vulnerable/Special Participant Populations Developing World *Bioethics* 5 (1) 30-53

Mason JK, McCall Smith RA, (1991) Law and Medical Ethics 3rd Edition. London *Butterworths* 359

Massarani L, (2008) Brazil breaks patent on HIV/AIDS drug *Science and*

Development Network <http://www.scidev.net> Accessed 9/9/08

Male B, (2005) HIV treatment advocacy-the African perspective *The African Eye Voice* 7: 8

Matlin S, Spence N, (2000) the Gender Aspects of the HIV/AIDS pandemic *World Health Organisation*

May W, (1975) Composition and Function of Ethical Committees *Journal of Medical Ethics* 1: 23-29

Medical Foundation for the Care of Victims of Torture (2007) Facts and Figures
<http://www.torturecare.org.uk> Accessed 11/09/08

Medicines and Health Care Products Regulations Agency (MHRA) available at
<http://www.mhra.gov.uk/publications/consultations/medicinesconsultations>

Medicines for Human Use (Clinical Trials) Regulations 2004 Statutory requirement for informed consent paragraph 3(1) of Part 1 of Schedule 1 to the regulations, implementing Article 2(j) of the EU directive
(www.hmso.gov.uk/si/si2004/20041031.htm)

Medical Research Council (1963) Responsibilities in Investigations in Human subjects

MRC Ethics Guide

Medical Research Council, (2002) MRC policy on antiretroviral therapy for people infected with HIV and involved in research in developing countries *MRC Ethics Guide*

The Medicines for Human Use (Clinical Trials Regulations) 2004 Informed Consent in Clinical Trials www.uk-legislation.hmso.gov Accessed 1/2/09

The Mental Capacity Act 2005 www.uk-legislation.hmso.gov Accessed 3/3/2013

Merck (2008) Post Trial Drug Access - Summary of Current Goals, Progress and Future Plans

Moberly T, (2007) Will drug trials be the same again? *The Pharmaceutical Journal* 276 (7393) 342

Montagnier L, Et al (1983) Isolation of a T. Lymphotropic retrovirus from a patient at risk of Acquired Immune deficiency Syndrome, *Science* 20

Moodley K, (2002) HIV Vaccine Trials Participation in South Africa-An Ethical Assessment *Journal of Medicine and Philosophy*, 27 (2) 197-215

Moss R, (2002) Clinical Trials and the 'Therapeutic Misconception'-the War on

Cancer *Townsend Letters for Doctors and Patients*

Mugenyi (2010) Routine v clinically driven laboratory monitoring of HIV antiretrovirals in Africa (DART): a random non-inferiority trial *The Lancet* 375 (9709): 123-31

Mulligan K (2000) Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection *Journal of Acquired Immune Deficiency Syndromes* 23 (1): 35-43

McDowell R (2012) Global action over the challenge to India's patent laws *HIV Treatment Bulletin* 13 (3/4)

McLean S, (1997) No consent means not treating patients with respect *British Medical Journal* 314: 1076

National Aids Manual (2007) Preventing mother to child transmission of HIV
<http://aidsmap.com> Accessed 12/09/2008

National AIDS Trust, Terrence Higgins Trust (2010) Hardship Fund Report: Poverty and HIV 2006-2009 Accessed February 2013
<https://www.tht.org.uk/binarylibrary/policy/povertyandhiv.pdf>

National Health Services (Charges to Overseas Visitors) Regulations (2011) *Crown Publications*

National Research Ethics Service (2009) Standard Operating Procedures *National Patient Safety Agency*

National Research Ethics Service (2009) Integrated Research Applications System Question A30-1 Informed consent *National Patient Safety Agency*

The National Sexual Health Strategy for England and Wales (2001) *Department of Health*

NHS Trusts and Primary Care Trusts (Sexually Transmitted Diseases) Directions 2000 *Department of Health*

Nelson RM, Merz JF, Voluntariness of consent for research: an Empirical and Conceptual Review *Medical Care Sep40 (9 supplement)*

Nicholson R, (2002) Who is Vulnerable in Clinical Research? *Bulletin of Medical Ethics* 181:19-22

Nuremberg Code available at <http://ohsr.od.nih.gov/guidelines/nuremberg.html>

Nursing and Midwifery Council (2008) Code of Professional Conduct *NMC Publications*

Nyambe M, (2005) Criminalisation of HIV transmission in Europe *The Global Network of People Living with HIV/AIDS Europe and Terrence Higgins Trust*

Peppercorn JM, Weeks JC, Cook FE, Joffe S (2004) Comparison of outcomes in cancer patients treated within and outside clinical trial: conceptual framework and structured review *Lancet* 363: 263-70

Phelan M, Parkman S, (2003) How to do it: work with an interpreter *British Medical Journal* 311: 555-557

Price MA et al (2011) Transmitted HIV type 1 drug resistance among individuals with recent HIV infection in East and Southern Africa *AIDS Research and Human retroviruses* 27(1): 5 -12

Quintiles (2010) Frequently Asked Questions for Clinical Trials Patients
<http://www.quintiles.com/for-patients-volunteers/faqs>

Accessed 28/11/11

Reeder R ed, (1999) Introduction to special issue on Vulnerable Populations
Bioethics Forum 15 (2)

R on the application of (YA) and the Secretary of State Neutral Citation Number:
(2009) EWHC CIV 225 *Crown Copyright*

Rosenheim ML, (1967) Supervision of the ethics of clinical investigations in institutions. Report of the committee appointed by the Royal College of Physicians of London *BMJ* 3: 429-30

Rothman D, (1992) Strangers at the Bedside. A history of how law and bioethics transformed medical decision making *Basic Books*

Royal College of Physicians (1984) Guidelines on the practice of ethics committees in medical research *RCP Press*

Royal College of Physicians (1986) Guidelines on the payment of volunteers in Phase 1 clinical trials *RCP Press*

Royal College of Physicians (2007) Guidelines on the practice of ethics committees in medical research with human participants *RCP Press*

Salaam T, (2005) AIDS Orphans and Vulnerable Children: Problems, responses and issues for congress *Congressional Research Services*

Shaffer DN, Yebi VN, Ballidawa JB, Et al (2006) Equitable treatment for HIV/AIDS clinical trials participants: a focus group study of patients, clinician researchers, and administrators in Western Kenya *Journal of Medical Ethics*, 32: 55-60

Silove D, Sinnerbrink I, Field A, Manicavasagar V, Steel Z (1997) Anxiety, depression and PTSD in Asylum Seekers: Association with Pre-Migration Trauma and Post-Migration Stressors *British Journal of Psychiatry* 170: 351-357

Singh J, (2006) How over-protectionism can evidence unethical outcomes: examples from South Africa *Research Ethics Review* 2 (2) 63-66

Smith R, (1997) Should the BMJ reject all studies that do not include informed consent? *British Medical Journal* 314:1059- 1060

Smith R, (1997) Mixed HIV status couples: Navigating the challenges of everyday life *Body Positive* October 1997

Sokol D, (2007) What would you do, Doctor? *British Medical Journal* 334: 853

Soome E, (2008) Completing the Picture: An examination of the Home Office's Country reports on the availability of HIV Treatment in Zambia, Malawi, Uganda, South Africa, Nigeria and Zimbabwe.

Standard Operating Procedures for Research Ethics Committees Version 3.4 (2007)
National Patient Safety Agency, National Research Ethics Service

Stead M, Eadie D, Gordon D, Angus K, (2004) 'Hello, hello- it's English I speak!': a Qualitative Exploration of Patients' Understanding of the Science of Clinical Trials
Journal of Medical Ethics 31:664-669

Stein (2003) Sorrow makes children of us all: A literature review of the psycho-social impact of HIV/AIDS on Children *CSSR working paper No.47*

Steingrover R, Pogany K, Fernandez Garcia E, Jurriaans S, Brinkman K, Schuitemaker H, Miedema F, Lange JM, Prins JM (2008) HIV-1 viral rebound dynamics after a single treatment interruption depends on time of initiation of HAART
AIDS 22 (13): 1583-1588

Steiner T, (2006) Guinea pig duties: 6 Non-consensual clinical research, *Research Ethics Review* 2 (2): 51-58

Stevenson J (2012) Destination Unknown: Where next? *African Health Policy Network*

Sugarman J, (2007) Ethical oversight of multinational collaborative research: lessons from Africa for building capacity and for policy *Research Ethics Review* 3: 84-86

The Terrence Higgins Trust (2010) Will I have to pay? Advice on getting NHS sexual health and HIV services for recent migrants and those of uncertain immigration status. *THT publication*

Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law (1949) 10: 2 181-182 *Washington D.C. U.S. Government Printing office*

Twyman R, (2004) A brief history of clinical trials *The Human Genome, Welcome Trust*

UNAIDS, (2006) Report on the Global AIDS Epidemic: The impact of AIDS on people and societies *United Nations Publications*

UNAIDS, (2007) A call to action: Children the missing face of AIDS *United Nations Publications*

UNAIDS, (2008) Report of the Global AIDS Epidemic *United Nations Publications*

UNAIDS, (2009) Towards Universal Access Scaling up priority HIV/AIDS interventions in the health sector *United Nations Publications*

UNAIDS, (2010) AIDS Epidemic Update *United Nations Publications*

UNICEF (2009) overview of Breast-feeding patterns: Proper Infant Feeding Practices are Key to Child Survival http://www.childinfo.org/breastfeeding_overview

Accessed 28/11/11

United Nations (1951) Geneva Convention Relating to the Status of Refugees *United Nations Refugee Agency*

Valcour V, Paul R, Chiao S, Wendelken LA, Millar B, (2011) Screening for cognitive impairment in human immunodeficiency virus *Clinical Infectious Diseases* 53: 836-842

Vollman J, Winau R, (1996) Informed consent in human experimentation before the Nuremberg code. *BMJ* 313: 1445- 1447

West J, Wright J, Tuffnell D, Jankowicz D, West R (2005) Do clinical trials improve Quality of care? A comparison of clinical processes and outcomes in patients in a clinical trial and similar patients outside a trial where both groups are managed according to a strict protocol *Quality and Safety in Health Care* 14 (3): 175-178

Whetten K, Reif S, Whetten R et al (2008) Trauma, Distrust and Stigma among HIV positive Persons: Impact for effective Care *Psychosomatic Medicine* 70 (5): 531-538

Wilkinson S, (2003) Bodies for sale: ethics and exploitation in the human body trade
Routledge

Wittkop L, Chêne G, Castro H. (2010) Impact of transmitted drug resistance (TDR) on virological and immunological response to initial combination antiretroviral therapy (cART) - EuroCoord-CHAIN joint project. *XVIII International AIDS Conference (AIDS 2010)*. Vienna, July 18-23, 2010. [Abstract THLBB108](#).

World CAB (2005) Report from the Community Advisory Board Meeting with the Indian Generic Drugs Industry <http://www.i-base.info>

World Economic Forum (2006) AIDS- everybody's business *UN publications*

World Health Organization (1993) Guidelines Requirements for Informed Consent
CIOMS/ WHO g.3

World Health Organization (1993) Guidelines payment of clinical trials participants
CIOMS/ WHO g.4

World Health Organization (2006) AIDS Epidemic Update *CIOMS/ WHO*

World Health Organization (2007) Towards Universal Access – treatment and care for

people living with HIV *CIOMS/ WHO*

World Health Organization (2008) Living 2008 Summit themes-Criminalisation of HIV
CIOMS/ WHO

World Health Organization (2009) HIV and Infant feeding: Revised Principles and
Recommendations *CIOMS/ WHO*

World Health Organization (2011) Mother to Child transmission of HIV *CIOMS/ WHO*

World Medical Association (1964) Declaration of Helsinki *World Medical Association*

World Medical Association (1996) Declaration of Helsinki, Recommendations Guiding
Medical Physicians in Biomedical Research Involving Human Subjects *World Medical
Association Article 2.3*

World Medical Association (2001) Declaration of Helsinki, Ethical Principles for
Medical Research Involving Human Subjects *World Medical Association Article c.29*

World Medical Association (2001) When are placebo controlled trials ethically
acceptable? Press Release www.wma.net

World Medical Association (2008) Declaration of Helsinki, Ethical Principles for

Medical Research Involving Human Subjects *World Medical Association* Article c.33

World Medical Association (2009) Statement on Genetics and Medicine Adopted by the 56th WMA general Assembly, Santiago, Chile, October 2005, and amended by the 60th WMA general assembly, New Delhi, India October 2009

<http://www.wma.net/en/30publications/10policies/g11/> Accessed 11/11/11

World Trade Organisation (1994) Agreement on Trade Related Aspects of Intellectual Property Rights *World Trade Organisation*

Yanofski J, Croakin P (2008) Choosing antidepressants for HIV and AIDS patients: Insights on safety and side effects *Psychiatry* 5 (5): 61-66

Zong Z, (2008) Should post-trials provision of beneficial experimental interventions be mandatory in developing countries? *Journal of Medical Ethics* 34: 188-192

